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Efficacy and Safety of Edoxaban and/or Colchicine for patients with COVID-19 managed in the out-of-hospital setting:
Rationale and design of the CONVINCE trial

Authors: Antonio Landi, MD, Nuccia Morici, MD, Pascal Vranckx, MD, PhD, Enrico Frigoli, MD, Luca Bonacchini, MD, Barbara Omazzi, MD, Moreno Tresoldi, MD, Claudio Camponovo, MD, Tiziano Moccetti, MD, Marco Valgimigli, MD, PhD

Affiliations:
From the Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland (A.L., E.F., M.V.); Department of Biomedical Sciences, University of Italian Switzerland, Lugano, Switzerland (A.L., M.V.); IRCCS S. Maria Nascente - Fondazione Don Carlo Gnocchi ONLUS, Milan, Italy (N.M.); the Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium (P.V.); Emergency Department, ASST Great Metropolitan Hospital Niguarda, Milan, Italy (L.B.); Emergency Unit, ASST Rhodense, Garbagnate Milanese, Italy (B.O.); Unit of General Medicine and Advanced Care, IRCCS San Raffaele Hospital, Milan, Italy (M.T.); Department of Anesthesiology, Clinica Ars Medica, Genolier Swiss Medical Network, Gravesano, Switzerland (C.C.); Studi Medici Riuniti & Partners, CH-6900 Lugano, Switzerland (T.M.); University of Bern, Bern, Switzerland (M.V.)

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Twitter handles: @vlgmrc (Marco Valgimigli), @antoniolandii (Antonio Landi)

Corresponding author:
Prof. Marco Valgimigli, MD, PhD
Cardiocentro Ticino Institute
Ente Ospedaliero Cantonale
Via Tesserete, 48
CH-6900, Lugano, Switzerland
Phone: +41 91 805 53 47
Fax: +41 91 805 30 34
e-mail: marco.valgimigli@eoc.ch

ABSTRACT (247 words)

Background. An excessive inflammatory response and a hypercoagulable state are not infrequent in patients with coronavirus disease-2019 (COVID-19) and are associated with adverse clinical outcomes. However, the optimal treatment strategy for COVID-19 patients managed in the out-of-hospital setting is still uncertain.
Design. The CONVINCE (NCT04516941) is an investigator-initiated, open-label, blinded-endpoint, 2×2 factorial design randomized trial aimed at assessing two independently tested hypotheses (anti-coagulation and anti-inflammatory ones) in COVID-19 patients. Adult symptomatic patients (≥18 years of age) within 7 days from reverse transcription-polymerase chain reaction (RT-PCR) diagnosis of SARS-CoV-2 infection managed at home or in nursery settings were considered for eligibility. Eligible patients fulfilling all inclusion and no exclusion criteria are randomized to edoxaban versus no treatment (anti-coagulation hypothesis) and colchicine versus no treatment (anti-inflammatory hypothesis) in a 1:1:1:1 ratio. The study had two co-primary endpoints (one for each randomization), including the composite of major vascular thrombotic events at 25 ± 3 days for the anti-coagulation hypothesis and the composite of SARS-CoV-2 detection rates at 14 ± 3 days by RT-PCR or freedom from death or hospitalizations (anti-inflammatory hypothesis). Study endpoints will be adjudicated by a blinded Clinical Events Committee. With a final sample size of 420 patients, this study projects an 80% power for each of the two primary endpoints appraised separately.
Conclusions. The CONVINCE trial aims at determining whether targeting anti-coagulation and/or anti-inflammatory pathways may confer benefit in COVID-19 patients managed in the out-of-hospital setting.

Trial Registration: ClinicalTrials.gov number, NCT04516941

Keywords: COVID-19; SARS-CoV-2; anticoagulant therapy; anti-inflammatory therapy; edoxaban; colchicine.

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a pandemic of unprecedented proportions, overwhelming worldwide healthcare organizations. The complex pathophysiological mechanisms of SARS-CoV-2 pulmonary infection and their impact on cardiovascular system have shed light on the role of an intense inflammatory response which involves (but is not limited to) the respiratory system and potentially triggering a "pro-thrombotic state" in certain patients.

An excessive inflammatory response has been documented in some COVID-19 patients, as assessed by a significant increase in C-reactive protein (CRP), erythrocyte sedimentation rate and interleukin (IL)-6 (1). Of note, IL-6 levels appeared to be associated with fibrinogen levels (2), highlighting that COVID-19-related "cytokine storm" may elicit the coagulation cascade activation and thrombosis. Furthermore, elevation of D-dimer and fibrin degradation products, thrombocythemia and prolonged thrombin time (2–4) together with the anatomopathological evidence of thrombosis *in situ* in the pulmonary vasculature (5,6) further supported the interconnection between thrombosis and inflammation in COVID-19 patients.

Within this pathophysiological framework, potentially successful treatments should target inflammatory pathways, coagulation cascade (7), or both. On one hand, colchicine exerts well-known anti-inflammatory and potential anti-viral properties through inhibition of the inflammosome signaling (IL-1β, IL-6 pathways), the reduction of neutrophil chemotaxis, neutrophil-platelet aggregation and, more interestingly, microtubule polymerization. Furthermore, recent literature data demonstrated a favorable safety profile with a reduction of cardiovascular ischemic events in patients with coronary artery disease (8–10). On the other hand, the optimal coagulation target of different anti-thrombotic regimens (which agents, what doses and for whom) is debatable in COVID-19 patients and limited data exist to guide treatments in the out-of-hospital setting. Therefore, we sought to assess the value of a direct factor X inhibitor namely edoxaban as prophylactic measure to mitigate the risk of venous and arterial thrombotic complications among patients with SARS-CoV-2 at high risk for developing COVID-19 -related morbidity and mortality.

This manuscript summarizes the design features of the *Efficacy and Safety of Edoxaban and/or Colchicine for patients with SARS-CoV-2 infection managed in the out-of-hospital setting: the CorONa VIrus edoxabaN ColchicinE (CONVINCE) trial,* an investigator-initiated, open-label, blinded-endpoint, 2×2 factorial design randomized clinical trial (RCT). We sought to investigate the safety and efficacy of edoxaban and/or colchicine

administration in SARS-CoV-2 infected patients who are managed outside the hospital with respect to the occurrence of fatal events, hospitalizations, major vascular thrombotic events (MVTE) or SARS- CoV-2 clearance rate by reverse transcription-polymerase chain reaction (RT-PCR).

RATIONALE FOR COLCHICINE

Colchicine has been traditionally used for the treatment of many rheumatic inflammatory diseases (11) (i.e. gout), representing also a valid treatment option for patients with acute pericarditis (12). The anti-inflammatory activity of colchicine in gout is mediated by the inhibition of cytoskeletal microtubule polymerization, with subsequent reduction of leukocytes expression of adhesion molecules, neutrophil migration and degranulation (13,14). Furthermore, colchicine may inhibit the inflammasome signaling (15) and improve endothelial function (16), whose role has been advocated as the common, final pathway of COVID-19 pathophysiology (17).

SARS-CoV-2 as other coronaviruses use the binding of viral proteins S to cellular receptors for host cells entry and factors acting on clathrin-mediated endocytosis (partially regulated by microtubules remodeling) could potentially decelerate their entry into target cells. As a result, from a theoretical standpoint, colchicine may exert anti-inflammatory and direct anti-viral properties through inhibition of microtubule polymerization. This preliminary evidence provided the rationale for several studies testing colchicine in patients with COVID-19 (**Table 1**). While there is accumulating evidence on the use of colchicine in hospitalized patients with moderate-to-severe COVID-19 (18–24), this treatment strategy has been tested only in a single study in the out-of-hospital setting (25). In the COLCORONA trial, colchicine was associated with significantly lower rates of the composite outcome of death or hospital admission compared with placebo among out-of-hospital patients with PCR-confirmed COVID-19 (25).

RATIONALE FOR EDOXABAN

Anticoagulant treatment has been recommended for hospitalized patients with COVID-19 to prevent thromboembolic cardiovascular events (7,26), especially considering that a subset of patients may experience arterial and venous events despite standard dose thromboprophylaxis (26,27). The prevalence of the latter

events may range from 15% to 85% in hospitalized patients with COVID-19 (28,29), depending on the considered study population (subjects hospitalized in intensive care unit or medical wards), outcome definitions, implemented diagnostic work-up (systematic screening or clinically-driven examinations) and different anti-thrombotic regimens.

Several RCTs have investigated the effects of prophylactic or therapeutic parenteral anticoagulation in COVID-19 patients with inconsistent results. Direct oral anticoagulants (DOACs) have been tested in four large RCTs investigating the effects of apixaban (31,32) or rivaroxaban (33,34) in hospitalized patients with COVID-19 or in symptomatic subjects managed outside the hospital (**Table 2**). While the ACTION (34) and ACTIV-B (31) trials demonstrated no significant clinical benefit of rivaroxaban and apixaban, respectively, the MICHELLE trial was the first study demonstrating a clinical advantage of rivaroxaban among patients discharged after COVID-19 hospitalization at increased thromboembolic risk (33). The inclusion of patients at different baseline risk and in different phases of the disease (treatment initiated during or after COVID-19 hospitalization versus patients managed outside the hospital) may account for these differences. In the largest FREEDOM COVID trial (32), among 3,398 non-critically ill patients hospitalized with COVID-19, no differences in the primary composite endpoint of all-cause mortality, requirement for intensive care unit level-of-care, systemic thromboembolism, or ischemic stroke were observed between therapeutic anticoagulation with apixaban or enoxaparin and prophylactic anticoagulation. Therapeutic anticoagulation was associated with a 30% and 25% relative risk reduction of all-cause death and intubation requiring mechanical ventilation, respectively (32). To date, no study investigated the effects of edoxaban, a direct factor X inhibitor, in hospitalized or non-hospitalized COVID-19 patients. Moreover, the value of targeting both therapeutic pathways (anticoagulation and/or anti-inflammatory therapy) in the out-of-hospital setting remains largely unsettled.

METHODS

Trial design and study hypotheses

The CONVINCE is an investigator-initiated, open-label, blinded-endpoint, 2×2 factorial design randomized trial, aiming at investigating the following hypotheses (tested independently):

1) *Anti-coagulation hypothesis.* Edoxaban is superior to no edoxaban treatment for occurrence of MVTE, defined as the composite of asymptomatic proximal deep-vein thrombosis (DVT), symptomatic

proximal or distal DVT, symptomatic pulmonary embolism (PE) or thrombosis, myocardial infarction (MI), ischemic stroke, non-central nervous system (CNS) systemic embolism and all-cause death.

2) *Anti-inflammatory hypothesis*. Colchicine is superior to no colchicine treatment for the SARS-CoV-2 clearance rates by RT-PCR or freedom from death or hospitalizations.

The CONVINCE trial planned to enroll approximately 420 patients across four European countries. The study sites include up to 30 hospitals or healthcare services with SARS-CoV-2 diagnostic facilities, usually (but not limited to) the emergency departments of academic or non-academic hospitals in Switzerland, Italy, Belgium and Spain.

This trial was conducted in compliance with the study protocol, the Declaration of Helsinki and Good Clinical Practice (as defined by the International Conference on Harmonization), as well as all national legal and regulatory requirements. Formal approval of the study was obtained from ethics committees at participating sites and written informed consent will be obtained from each patient, prior to study randomization. The trial has been registered in clinicaltrials.gov (NCT04516941).

Study population

Symptomatic patients (≥18 years of age) with laboratory-confirmed SARS-CoV-2 infection (within 7 days from RT-PCR diagnosis) managed at home or in nursery settings will be considered for eligibility. Patients with blood dyscrasias, hepatic disease (associated with coagulopathy and clinically relevant bleeding risk), other conditions associated with high risk of major bleeding, uncontrolled severe hypertension, creatinine clearance (CrCl) <15 ml/min, ongoing or planned treatment with dual anti-platelet therapy (DAPT), parenteral or oral anticoagulants will be excluded. Details regarding the study entry criteria are presented in **Table 3** and the study flow diagram (**Figure 1**).

Study treatments and comparators

For the anti-coagulation hypothesis, the study intervention is edoxaban 60 mg once daily (od) or 30 mg od (in patients with CrCl ≤ 50 ml/min or body weight ≤60 kg) from randomization to the study closure visit (SCV, at day 25 ±3), as shown in **Figure 2**. Among patients who are concomitantly treated with P-Glycoprotein (P-

gp) inhibitors (such as ciclosporin, dronedarone, erythromycin, or ketoconazole), the recommended edoxaban dose should be 30 mg od.

For the anti-inflammatory hypothesis, the study intervention is colchicine 0.5 mg (bis in die [bid] for the first 3 days and then od) from randomization to 14±3 days (**Figure 2**). In patients with CrCl between 15 and 30 ml/min, the loading dosage is 0.5 mg od while the maintenance dosage remains unchanged. In case of concomitant treatment with P-gp inhibitors and/or CYP3A4 inhibitors (such as erythromycin and clarithromycin), colchicine regimen will be interrupted. At 14±3 days study visit, SARS-CoV-2 clearance rates by RT-PCR will be assessed as part of the composite primary endpoint for the colchicine versus no colchicine treatment. In patients who have successfully cleared SARS-CoV-2, no further treatment with colchicine is foreseen per protocol. Conversely, patients with no RT-PCR evidence of SARS-CoV-2 clearance at 14 ±3 days will continue the treatment until 25 ±3 days study visit. Further treatments are at discretion of the treating physician.

Treatment adjustments in case of (new onset) indication for anticoagulation

Patients with ongoing or planned indication to oral or parenteral anticoagulation will be excluded from this study. However, whether indication for anti-coagulation occurs during the study period (i.e. new onset atrial fibrillation with CHA_2DS_2-VASc score >1 or any thrombotic event occurrence), anticoagulation should be initiated as early as possible in the investigator's opinion. If the patient was previously randomized to edoxaban, this treatment strategy may be continued as prophylactic or therapeutic measure of the new onset clinical condition. In absence of previous allocation to the edoxaban arm, the choice of oral (DOACs or Vitamin K antagonists) or parenteral anticoagulant regimen is at the discretion of the treating physician.

In case of new hospitalizations or bed rest, prophylactic anticoagulation regimen remains at discretion of the treating physician in the no-edoxaban arm, whereas anti-coagulant regimen should be continued as per protocol in the edoxaban group. These treatment adjustments will be analyzed as an integral "per protocol" part of implementation of randomized treatment regimen.

Treatment adjustments in case of (new onset) bleeding/ischemic events or blood dyscrasia

The occurrence of new onset bleeding/ischemic events or blood dyscrasia during the study period will require adjustments of the treatment strategies. In case of Bleeding Academic Research Consortium (BARC) type 2 bleeding, the randomized treatment regimen should be continued, while discontinuation of edoxaban treatment is mandatory in case of BARC 3 bleeding.

In case of stroke, MI, confirmed DVT, PE/thrombosis or non- CNS systemic embolism further antithrombotic regimens are left at the investigator's discretion. In patients requiring surgery or percutaneous procedures, randomized treatments should be resumed as soon as the indication of temporary discontinuation is resolved.

In patients in whom blood dyscrasia (low white blood cell, hemoglobin and/or platelet count) occurs during the study period, patients randomized to colchicine should permanently interrupt the treatment regimen. In patients randomized to the edoxaban arm with new-onset anemia, occult source of bleeding should be screened in the absence of clinically overt bleeding.

Screening and randomization

The study design is presented in **Figure 1**. Eligible patients meeting all inclusion and no exclusion criteria will be randomized firstly to edoxaban versus no treatment and secondly to colchicine versus no treatment in a 1:1:1:1 ratio. The randomization procedure is programmed into the electronic Case Report Form (eCRF) by the trial statistician, based on a computed-generated random list of numbers in random blocks of 4 to 8, stratified by clinical site and sex. If the subject is randomized to edoxaban and/or colchicine, the allocated regimen should be initiated within 48 h after randomization.

In addition to the randomization visit, there are four scheduled follow-up visits: at 7±3 and 21±3 days (phone contact or video call if technically feasible) and at 14 ±3 and 25±3 days (visits to outpatient clinic). Patients with persisting symptoms at 25±3 days visit will be followed-up on a monthly basis by means of phone calls until at least 7 days after symptom resolution. This is deemed necessary in order to collect global disease burden as well as complete follow-up of all patients until serious adverse events (SAEs) resolution. In one center (Lugano, Switzerland) remote monitoring is performed by Hospithome SA (Lugano, Switzerland).

Study endpoints

This study has 2 co-primary endpoints (one for each randomization).

The co-primary endpoint for the anti-coagulation hypothesis (edoxaban vs. no active treatment) is MVTE at 25 ± 3 days defined as the composite of symptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic PE or thrombosis, MI, ischemic stroke, non- CNS systemic embolism and death. Systematic screening of MVTE will be performed through bilateral lower extremity venous ultrasonography at 25 ± 3 days, although clinically indicated testing will be at the discretion of the treating physicians.

The co-primary endpoint for the anti-inflammatory hypothesis (colchicine vs no active treatment) is the composite of SARS-CoV-2 detection rates at 14 ± 3 days by RT-PCR or freedom from death or hospitalizations.

Key secondary efficacy endpoints include the need for non-invasive or invasive ventilation, need for oxygen therapy, body temperature kinetics, need for analgesics, hospitalization and total days in the hospital, any combination of the above endpoints, each component of the primary endpoint as well as pre-specified composite endpoints at the time all SAEs have come to a resolution, global burden of disease (duration and severity of symptoms, morbidly and mortality) until symptoms resolution, impact of both treatments on coagulation and inflammatory biomarkers, EKG changes, high-sensitive cardiac Troponin (hs-cTn) levels, bleeding events according to BARC (35) and ISTH (36) classification. Study endpoints are presented in **Table 4**.

Statistical considerations and sample size calculation

The rates of primary endpoints are estimated as the cumulative incidence from the date of randomization to 14±3 days (anti-inflammatory hypothesis) and to 25±3 days (anticoagulation hypothesis) by Kaplan-Meier methods. The relative risk ratio (edoxaban vs. no edoxaban and colchicine vs. no colchicine) with respect to the rates of the primary efficacy endpoints will be estimated based on non-stratified estimators using Mantel-Haenszel weights and the corresponding non-stratified asymptotic 2-sided 95% confidence intervals.

Main analysis of the primary endpoints will be performed in the modified intention-to-treat (mITT) population, including randomized patients in whom at least 1 dose of study medication is administered with an adequate assessment of MVTE (edoxaban versus no treatment arm) or an adequate assessment of SARS-CoV-2 infection rate by RT-PCR (colchicine versus no treatment comparison). Sensitivity analyses will be performed

in the per-protocol population (patients meeting all inclusion and no exclusion criteria in whom the randomized treatment was implemented within 48 hours) and on-treatment populations (randomized patients in whom overall adherence to protocol mandated medications is more than 80% or less than 120%).

The CONVINCE trial planned to enroll a total of 420 patients relying on the following considerations. A total of 204 patients per group will provide 80% power to assess the superiority of edoxaban compared to no edoxaban on the composite endpoint of MVTE or death at day 25±3 days after randomization in the mITT population, assuming an event rate of 8% and 2% in the no edoxaban and edoxaban group, respectively, with an alpha error set at 5.0%. A total of 167 patients per group will provide 80% power to assess the superiority of colchicine as compared to no colchicine on the SARS-CoV-2 detection rates or death or hospitalizations at day 14±3 days after randomization in the mITT population assuming an event rate of 50% and 35% in the no colchicine and colchicine group, respectively, with an alpha error set at 5.0%.

The following subgroups analysis are pre-specified: age ≥ or < 65 years, female vs. male gender, high versus no high-risk patients, CrCl ≥50 ml/min or < 50 ml/min or fulfilment of other dose reduction criteria for edoxaban, symptoms duration related to COVID-19 related, the presence or absence of each high-risk criteria, allocation to edoxaban for colchicine randomization and to colchicine for edoxaban randomization. High risk criteria include active malignancy, prior MI, history of congestive heart failure (CHF), diabetes mellitus, D-dimers above the upper limit of normal values, active smoking, chronic obstructive pulmonary disease or other chronic lung diseases and prior VTE.

Clinical event adjudication committee

Clinical events adjudication of all endpoints will be performed by the clinical event committee (CEC) which is composed by qualified physicians who are not investigators in the trial. The CEC is responsible for adjudicating all potential endpoint events as well as the reasons for hospitalizations, remaining blinded to all treatment regimens throughout the adjudication process and the study period. Clinical events definitions are presented in the **Supplementary Material**.

Executive, steering, and data safety monitoring committees

The Executive Committee (ExC) is responsible for the study oversight. The Steering Committee is composed by the ExC members and national lead investigators. The operational committee is responsible for executing and implementing study procedures under the supervision of the ExC. Endpoint-related and unrelated SAEs were periodically reviewed and analyzed by an independent data safety monitoring board (DSMB). Members of this board were not affiliated with any site enrolling patients into the CONVINCE study and did not participate in the trial.

A CRITICAL APPRAISAL OF AVAILABLE EVIDENCE

Inflammation and thrombosis are tightly interrelated pathophysiological processes that considerably influence each other: pro-inflammatory cytokines (when inappropriately released or in excess, the so-called "cytokines storm") may perturb the balance of the coagulation cascade into a pro-thrombotic state, which in turn significantly potentiates inflammatory pathways in a vicious circle (37,38). There is emerging evidence suggesting that COVID-19 related morbidity and mortality represents the result of the complex pathway of this "thrombo-inflammatory storm" (39–41).

The CONVINCE trial will help answer important questions about the out-of-hospital management of COVID-19 patients, providing further insights into the anti-coagulation and anti-inflammatory hypotheses. First, it is the only study testing two treatment strategies targeting both inflammation (colchicine) and coagulation (edoxaban) pathways in the entire spectrum of non-hospitalized COVID-19 patients. For each experimental treatment, an independent composite endpoint has been developed and no interaction between the two is expected, making the 2x2 factorial design suitable to test two treatment options in the same patient population. Second, the chosen endpoint for edoxaban arm investigates the potential impact of this treatment on a broad variety of thrombotic disorders occurring in the venous or arterial systems, whereas the primary endpoint for colchicine captures the possible effect of colchicine on virus clearance or clinical deterioration resulting in hospitalizations or death. Third, surveillance screening of VTE (through lower extremity venous ultrasonography at 25±3 days) and serial quantification of myocardial injury (at baseline, 14±3 and 25±3 days) will provide useful insights into the true prevalence and clinical significance of such complications and the possible impact of "early" anti-inflammatory and anti-coagulation regimens in out-of-hospital patients. Recently, a retrospective, observational study provided initial evidence regarding the frequency and impact of

arterial and VTE events on 30-day clinical outcomes in COVID-19 patients managed in the out-of-hospital setting (42). The lower-than-expected rate of MVTE in this study was probably underestimated since active surveillance screening of VTE was not performed, at variance with the CONVINCE trial. Moreover, baseline study features revealed a low-risk profile of this population (mean age 44.8 years, diabetes 9%, active malignancy 2%, history of coronary artery disease and CHF 3.1% and 1.2% respectively) (42), which make these findings less generalizable to the wide spectrum of non-hospitalized COVID-19 patients.

Some design features and limitations of the CONVINCE trial deserve further attention. First, considering the unique and fast-evolving conditions caused by COVID-19, we designed an open-label randomized trial, mainly due to time restraints. However, all outcomes will be adjudicated by a CEC blinded to treatment assignment. Second, primary and secondary endpoints were appraised up to 25±3 days after randomization. Although a longer follow-up may be desirable in this setting, available evidence suggests that the first 2-3 weeks represent the highest-risk period in terms of MVTE and the median period of viral genome detectability for COVID-19 patients is 11 days (IQR, 8-14.3 days) (43). Moreover, patients with persisting symptoms at the SCV will be followed-up on a monthly basis by means of phone calls until at least 7 days after symptoms resolution, in order to collect global disease burden and complete follow-up data.

STUDY ORGANIZATION, TIMELINES AND CONCLUSIONS

This study is an investigator-driven clinical trial sponsored by Insel Gruppe AG (Bern, Switzerland), and supported by a research grant from Daiichi-Sankyo. The co-sponsor is Azienda Socio-Sanitaria Territoriale of Lecco (Italy). Independent data management, central data review and statistical analysis are performed by Advice Pharma (Milan, Italy). The first study patient was randomized in March 2021. On September 2022, the study was prematurely halted by drug manufacturer after recruitment of 60 patients.

The CONVINCE trial will help to determine whether targeting both anti-coagulation and anti-inflammatory pathways may confer benefit in COVID-19 patients managed in out-of-hospital setting. The optimal management of these patients represents a key point in order to prevent future overwhelming of healthcare systems. The unique features of this study, including the 2×2 factorial design and the inclusion of the entire spectrum of non-hospitalized subjects with SARS-CoV-2 infection will add to the body of evidence to guide treatment strategies for COVID-19 patients.

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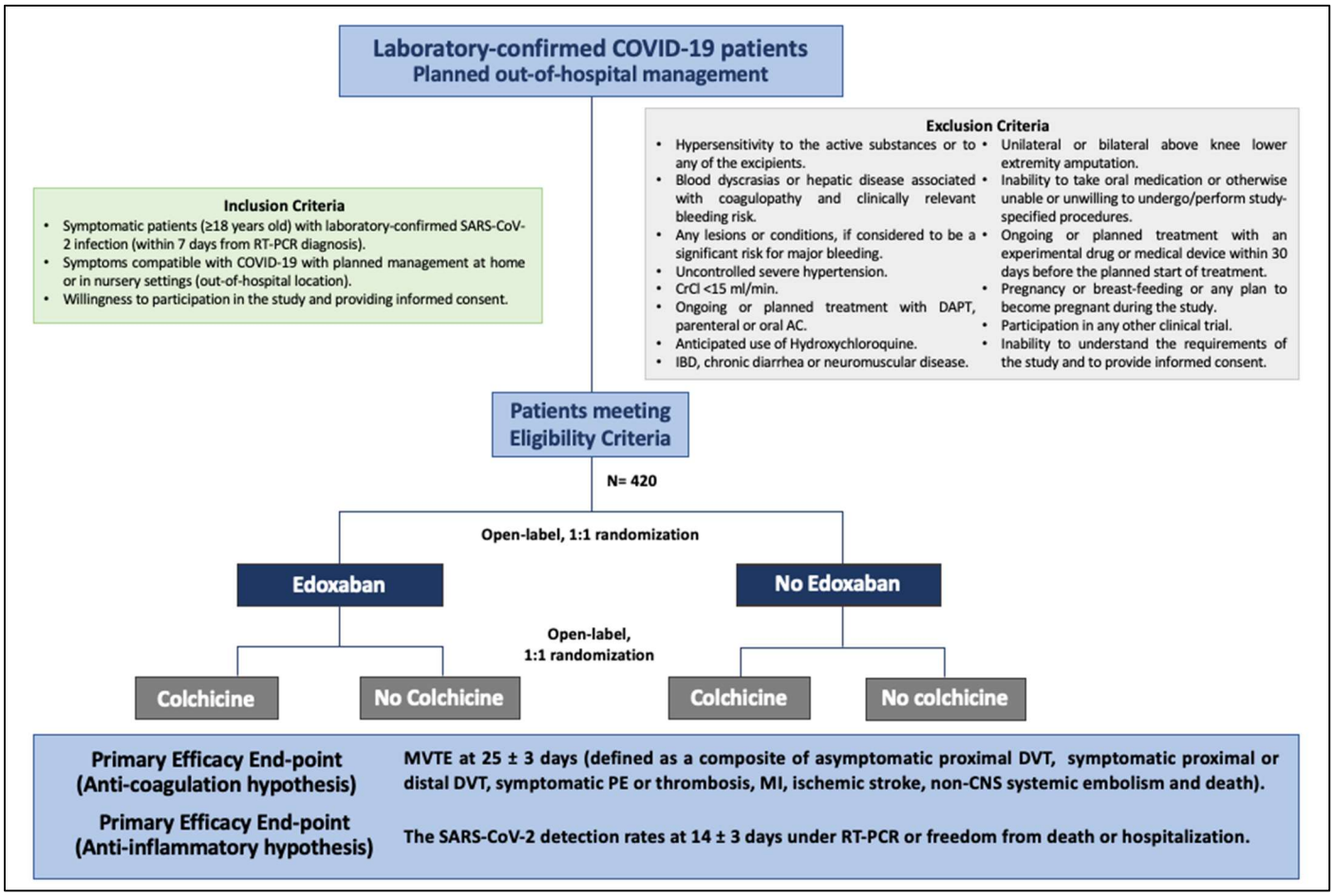
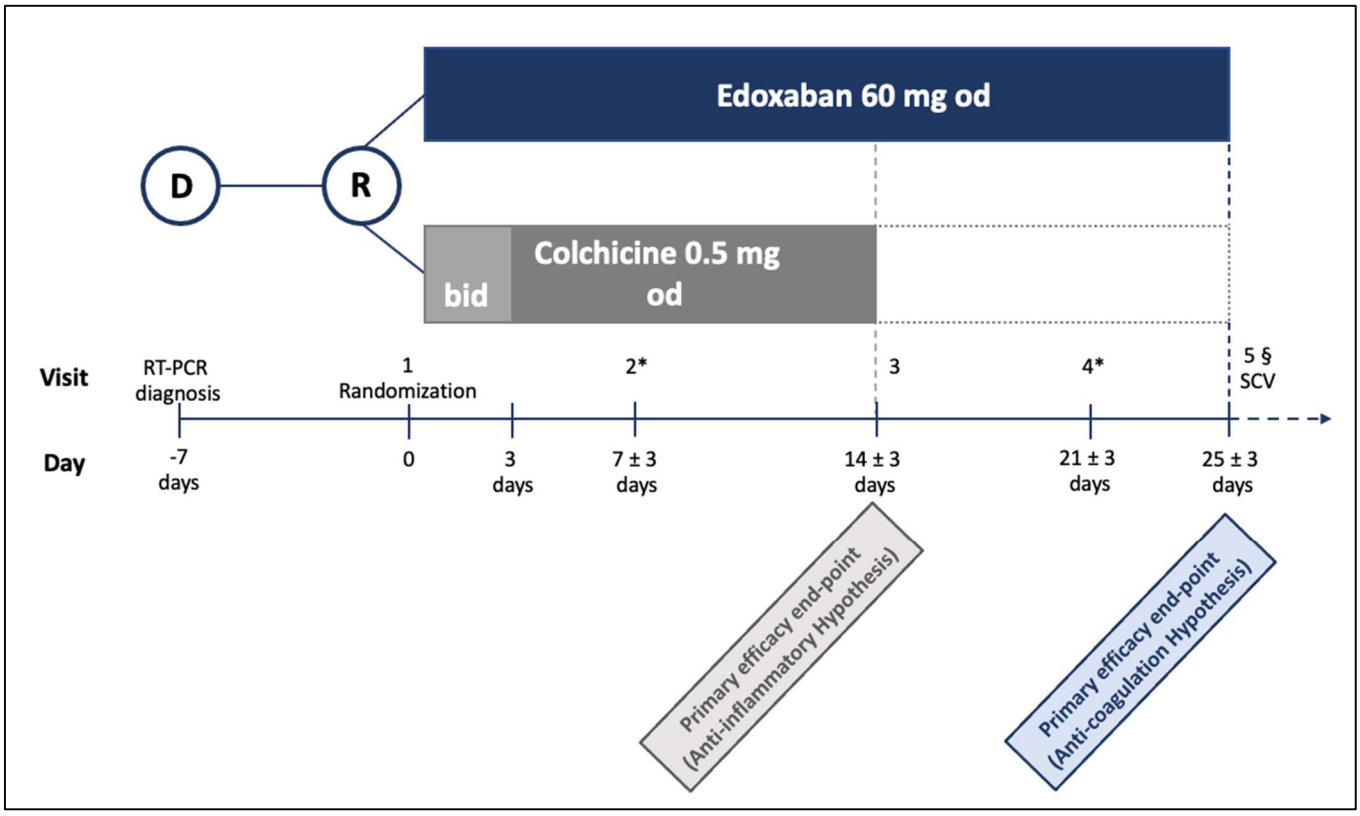
FIGURE LEGENDS

Figure 1. CONVINCE study flow diagram.



Abbreviations: AC= anti-coagulant; CrCl= creatinine clearance; COVID-19= coronavirus disease-2019; CNS= central nervous system; DAPT= dual antiplatelet therapy; DVT= deep vein thrombosis; MI= myocardial infarction; MVTE= major vascular thrombotic events; PE= pulmonary embolism.

Figure 2. Study treatments. * phone contact or video call (if technically feasible). § Patients with persisting symptoms at 25±3 days (SCV) will be followed-up on a monthly basis by means of phone calls until at least 7 days after symptoms resolution.



Abbreviations: od=once daily; bid= bis in die; RT-PCR= reverse transcription - polymerase chain reaction; SCV= study closure visit.

TABLES

Table 1. Main randomized clinical trials investigating the use of colchicine in patients with coronavirus disease 2019 (COVID-19).

Trial, year	Sample size	Study population	Intervention	Control	Primary endpoint (s)	Main results
COLCORONA, 2021 (25)	4,488	Patients with COVID-19 (diagnosed by PCR testing or clinical criteria) managed in the out-of-hospital setting, aged more than 40 years old and with at least one high-risk characteristic.	Colchicine 0.5 mg b.i.d. for the first 3 days, followed by 0.5 mg o.d. for 27 days thereafter	Placebo	The composite of death or hospital admission for COVID-19 at 30 days.	No significant differences in the overall cohort. Among PCR-confirmed COVID-19, colchicine resulted in lower rates of the primary endpoint compared with placebo (OR: 0.75, 95% CI: 0.57-0.99; p=0.042).
ECLA PHRI COLCOVID, 2021 (18)	1,279	Hospitalized patients with confirmed or suspected moderate-to-severe COVID-19.	Colchicine 1.5 mg loading dose + 0.5 mg within 2 hours followed by 0.5 mg b.i.d. up to hospital discharge or 14 days (whichever occurred first)	SoC	The composite of a new requirement for mechanical ventilation or death evaluated at 28 days.	No significant differences in the primary endpoint (HR, 0.83; 95% CI: 0.67-1.02; p=0.08).
RECOVERY, 2021 (19)	11,340	Clinically suspected or laboratory confirmed COVID-19 patients who are hospitalized and at low risk.	Colchicine 1 mg loading dose + 0.5 mg 12 h later followed by 0.5 mg b.i.d. for 10 days in total or until discharge.	SoC	All-cause mortality.	No differences in the rate of all-cause mortality between groups (RR: 1.01; 95% CI: 0.93- 1.10; p=0·77). Consistent results were observed in all prespecified subgroups of patients.
GRECCO-19 2020 (20)	105	Hospitalized patients with COVID-19 confirmed by RT-PCR, with body temperature ≥ 37.5 °C and at least 2 of the following: sustained coughing, sore throat, anosmia, and/or ageusia, fatigue and/or tiredness, arterial oxygen	Colchicine 1.5 mg loading dose + 0.5 mg within 1 hour followed by 0.5 mg b.i.d. up to hospital discharge or 21 days (whichever occurred first)	SoC	(1) Maximum level of hs-cTn (2) Time for CRP to reach more than 3 times the URL: (3) Time to deterioration by 2 points on a 7-grade clinical status scale.	(1) Maximum level of hs-cTn: 0.008 ng/ml (colchicine) vs 0.0112 ng/ml (control group), p=0.34 (2) Time for CRP to reach more than 3 times the URL: 4.5 mg/dl (colchicine) vs 3.1 mg/dl (control), p= 0.73 (3) Time to deterioration by 2 points on a 7-grade clinical status scale: 1.8% (colchicine) vs 14% (control), p= 0.02

		partial pressure <95% on room air.				
Lopes MI et al., 2021 (21)	75	Moderate to severe COVID-19 diagnosed by RT-PCR or CT-scan.	Colchicine 1.0 mg followed by 0.5 mg thrice daily for 5 days	Placebo	(1) Death (2) Need for supplemental oxygen (3) Time of hospitalization (4) Need for ICU admission (5) Length of ICU stay.	(1) Death: Two patients died in the placebo group. (2) Time for need of supplemental oxygen: 4 days (colchicine) vs 6.5 days (control), p<0.001 (3) Time of hospitalization: 7.0% (colchicine) vs 9% (control), p= 0.003 (4) Need for ICU admission: 2 and 4 patients in the colchicine and placebo groups, respectively (excluded from the analysis) (5) Length of ICU stay: 12 days (colchicine) vs 11 days (control)
COLVID-19, 2023 (22)	152	Hospitalized patients with COVID-19 confirmed by RT-PCR; clinical/instrumental diagnosis of pneumonia; oxygen saturation at rest in ambient air ≤94% and a PaO2/FiO2 (P/F) ratio of 350 to 200 mmHg	Colchicine 0.5 mg three times daily for maximum days or until hospital discharge	SoC	The composite of need for mechanical ventilation, ICU, or death at 30 days.	No difference in the rate of the co-primary endpoint between patients treated with colchicine compared to controls (14.3% vs 13.3%, P=ns).
Kasiri et al., 2023 (23)	110	Hospitalized patients with severe COVID-19	Colchicine (2 mg loading dose followed by 0.5 mg twice daily for 7 days)	Placebo	Clinical response as ordinal scale of 1 or 2	58.8% in the control group versus 63.6% of patients in the colchicine responded to treatment within 7 days (OR: 1.23, 95% CI: 0.560–2.68; p = 0.61).
COLSTAT trial, 2023 (24)	250	Non-critically ill hospitalized patients with COVID-19.	Colchicine (0.6mg b.i.d. for 3 days followed by 0.6mg o.d.) and high intensity rosuvastatin (40 mg daily) up	SoC	The composite of progression to severe COVID-19 disease or arterial/venous	No significant differences in the primary study endpoint: 15.2% (colchicine + rosuvastatin group) vs 8.8% (SoC).

			to hospital discharge or 30 days (whichever came first)		thromboembolic events (ischaemic stroke, MI, or PE) at 30 days	The trial was terminated early for futility.

Abbreviations: b.i.d., bis in die; CI, confidence interval; CRP, C-reactive protein; *CT, computed tomography; DVT, deep venous thrombosis; HR, hazard ratio; hs-cTn,* high-sensitivity cardiac troponin; *ICU, intensive care unit; MI, myocardial infarction; o.d., once daily; OR, odds ratio; PE, pulmonary embolism; RR, rate ratio; RT-PCR, real time- polymerase chain reaction; SoC, standard of care; URL, upper reference limit.*

Table 2. Main randomized clinical trials investigating the use of direct oral anticoagulants (DOACs) in patients with coronavirus disease 2019 (COVID-19).

	ACTION (34)	**ACTIV-4B** (31)	**MICHELLE** (33)	**FREEDOM COVID** (32)
Year	2021	2021	2022	2023
Sample size	615	657	320	3,398
Population	Patients hospitalized for COVID-19 with increased levels of D-Dimer	Symptomatic COVID-19 patients managed in the out-of-hospital setting	Patients discharged after COVID-19 hospitalization at increased VTE risk defined as IMPROVE VTE score of ≥4 or 2–3 with a D-dimer >500 ng/mL.	Non-critically ill patients hospitalized with COVID-19
Intervention	Therapeutic anticoagulation: rivaroxaban 20 mg or 15 mg o.d., LMWH or UFH	Therapeutic anticoagulation: apixaban 5 mg b.i.d.	Rivaroxaban 10 mg o.d.	- Therapeutic-dose enoxaparin (1mg/kg s.c. o.d.; 1mg/kg o.d. for CrCl <30 mL/min) - Therapeutic-dose apixaban (5mg b.i.d.; 2.5 mg b.i.d. for patients with at least 2 of 3 of the following: age ≥ 80 years, weight ≤ 60 kg or serum Cr ≥ 1.5 mg/dL).
Control	Prophylactic anticoagulation: enoxaparin or UFH	Prophylactic anticoagulation (apixaban 2.5 mg b.i.d.); placebo	No anticoagulation.	Prophylactic-dose enoxaparin (40mg o.d.; 30mg for CrCl <30 mL/min).
Primary endpoint(s)	The composite of time to death, duration of hospitalization or duration of supplemental oxygen	The composite of all-cause death, symptomatic VTE or arterial thromboembolism, MI, stroke, or hospitalization for a cardiovascular or pulmonary cause	The composite of VTE and arterial thrombotic events (MI, non-hemorrhagic stroke, major adverse limb events and CV death)	The composite of all-cause mortality, requirement for ICU level-of-care, systemic thromboembolism, or ischemic stroke
Main results	No differences in the primary composite endpoint with therapeutic compared with prophylactic anticoagulation.	No differences in the primary endpoint between groups.	Rivaroxaban treatment resulted in significantly lower rates of the composite endpoint compared with no anticoagulation (RR 0.33, 95% CI 0.12–0.90; p=0.03). No	No differences in the primary endpoint with therapeutic-dose compared with prophylactic-dose anticoagulation. Therapeutic anticoagulation resulted in lower rates of all-cause mortality (HR:

	Major or clinically relevant non-major bleeding was significantly higher in the therapeutic compared with prophylactic anticoagulation group (RR: 3.64; 95% CI: 1.61–8.27; p=0.001).	The study was terminated after enrollment of 9% of participants due to lower than anticipated event rates.	significant differences in major bleeding were detected between the two study groups.	0.70; 95% CI: 0.52-0.93; P= 0.01) and intubation (HR: 0.75; 95% CI: 0.58-0.98; P = 0.03) compared with prophylactic-dose enoxaparin.
Follow-up	30 days	45 days	35 days	30 days

Abbreviations: b.i.d., bis in die; CI, confidence interval; Cr, creatinine; CrCl, creatinine clearance; HR, hazard ratio; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; MI, myocardial infarction; o.d., once daily; VTE, venous thromboembolism; RR, relative risk.

Table 3. Inclusion and exclusion criteria.

Inclusion criteria	1. Symptomatic patients (≥18 years-old) with laboratory-confirmed SARS-CoV-2 infection (within 7 days from RT-PCR diagnosis). 2. Symptoms compatible with COVID-19 with planned management at home or in nursery settings (out-of-hospital location). 3. Willingness to participation in the study and providing informed consent.
Exclusion criteria	1. Hypersensitivity to the active substances or to any of the excipients. 2. Patients with blood dyscrasias (i.e. agranulocytosis, aplastic anaemia and thrombocytopenia). 3. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including Child-Pugh C cirrhosis with portal hypertension. 4. Lesions or conditions considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial hemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. 5. Uncontrolled severe hypertension. 6. CrCl <15 ml/min. 7. Ongoing or planned treatment with parenteral or oral AC. 8. Need for DAPT consisting of aspirin and an oral $P2Y_{12}$ inhibitor. 9. Anticipated use of Hydroxychloroquine. 10. Inflammatory bowel disease or chronic diarrhea or neuromuscular disease. 11. Unilateral or bilateral above knee lower extremity amputation. 12. Inability to take oral medication or otherwise unable or unwilling to undergo/perform study- specified procedures. 13. Patients who have received or will receive an experimental drug or an experimental medical device within 30 days before the planned start of treatment. 14. Pregnancy or breast-feeding or any plan to become pregnant during the study. Women (and men, for colchicine group only) with child-bearing potential not using adequate birth control method (as highly effective method of birth control oral contraception with inhibition of ovulation is recommended. If oral contraception with inhibition of ovulation is not feasible, another highly effective birth control methods as intrauterine device can be considered). 15. Participation in any other clinical trial. 16. Inability to understand the requirements of the study and to provide informed consent.

Abbreviations: AC= anti-coagulant; COVID-19= coronavirus disease-2019; CrCl= creatinine clearance; DAPT= dual antiplatelet therapy; RT-PCR= reverse transcription - polymerase chain reaction.

Table 2. Study endpoints.

Primary endpoints	**Edoxaban vs. no active treatment**	MVTE at 25±3 days defined as a composite of: - Asymptomatic proximal DVT - Symptomatic proximal or distal DVT - Symptomatic PE or thrombosis - MI - Ischemic stroke - Non-CNS systemic embolism - Death
	Colchicine vs. no active treatment	The SARS-CoV-2 detection rates at 14±3 days by RT-PCR or freedom from death or hospitalization
Secondary endpoints	- Each component of the co-primary endpoints. - Need for non-invasive or invasive ventilation. - Need for oxygen therapy. - Body Temperature kinetics. - Need for analgesics including NSAIDs and/or paracetamol. - Need for hospitalization and total days in the hospital. - Any combination of the above endpoints. - Each component of the primary endpoints as well as pre-specified composite endpoints at the time all SAEs have come to a resolution. - Global burden of disease defined as duration and severity of symptoms, morbidly and mortality until symptoms resolution. - Impact of either intervention on coagulation and inflammatory biomarkers including IL-6, CRP, D-dimers, sCD40L, Fibrinogen, Factor X activity and Factor XIa. - EKG analyses for QT segment measures and for detection of EKG changes associated to myo-pericarditis. - Hs-Tn levels. - Bleeding endpoints according to BARC 2, 3 or 5 and ISTH major and clinically relevant non-major bleeding.	

Abbreviation: BARC= Bleeding Academic Research Consortium; CNS= central nervous system; CRP= C-reactive protein; DVT= deep-vein thrombosis; EKG= electrocardiogram; hs-Tn= high sensitive- Troponin; IL-6= Interleukin-6; MI= myocardial infarction; ISTH= International Society on Thrombosis and Haemostasis; MVTE= Major vascular thrombotic events; NSAIDs= non-steroidal anti-inflammatory drugs; PE= pulmonary embolism; RT-PCR= reverse transcription - polymerase chain reaction; SAEs= serious adverse events.