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Medically Ill hospitalized Patients for COVID-19 THrombosis Extended ProphyLaxis with rivaroxaban ThErapy: Rationale and Design of the MICHELLE Trial ☆

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Background The devastating Coronavirus disease (COVID-19) pandemic is associated with a high prothrombotic state. It is unclear if the coagulation abnormalities occur because of the direct effect of SARS-CoV-2 or indirectly by the cytokine storm and endothelial damage or by a combination of mechanisms. There is a clear indication of in-hospital pharmacological thromboprophylaxis for every patient with COVID-19 after bleed risk assessment. However, there is much debate regarding the best dosage regimen, and there is no consensus on the role of extended thromboprophylaxis.

Design This study aims to evaluate the safety and efficacy of rivaroxaban 10 mg once daily for 35 ± 4 days versus no intervention after hospital discharge in COVID-19 patients who were at increased risk for VTE and have received standard parenteral VTE prophylaxis during hospitalization. The composite efficacy endpoint is a combination of symptomatic VTE, VTE-related death, VTE detected by bilateral lower limbs venous duplex scan and computed tomography pulmonary angiogram on day 35 ± 4 posthospital discharge and symptomatic arterial thromboembolism (myocardial infarction, nonhemorrhagic stroke, major adverse limb events, and cardiovascular death) up to day 35 ± 4 posthospital discharge. The key safety outcome is the incidence of major bleeding according to ISTH criteria.

Summary The MICHELLE trial is expected to provide high-quality evidence around the role of extended thromboprophylaxis in COVID-19 and will help guide medical decisions in clinical practice.[1] (Am Heart J 2021;242:115–122.)

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19, is a prothrombotic disease. It is unclear if the coagulation abnormalities occur because of the direct effect of SARS-CoV-2 or indirectly by the cytokine storm or by a combination of mechanisms.[1] The endothelial damage observed in COVID-19 patients coupled with multiple coagulopathic pathways leads to increased risk of thrombotic complications, including arterial, venous thromboembolic, and in-situ arterial microthrombi.[2]

Growing evidence of higher-than-expected rates of thrombotic events complicating COVID-19 has

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emerged,[3] mainly pulmonary embolism and primary pulmonary thrombosis. One out of every 3 or 4 patients admitted to the intensive care unit with COVID-19 is expected to complicate with a thrombotic event.[4-6] Observational data suggest the benefit of anticoagulation for hospitalized COVID-19 patients irrespective of the confirmation of a thrombotic event,[7] and many ongoing clinical trials are recruiting patients to test different anticoagulation regimens in this clinical setting.[8]

There is a clear indication of in-hospital pharmacological thromboprophylaxis for every patient with COVID-19 after bleed risk assessment.[9] However, there is much debate regarding the ideal anticoagulant and the correct dose to be used. Early retrospective data suggest a lack of postdischarge thrombotic events; however, more recent large-scale registry data suggest high event rates of major thromboembolism and mortality.[10-12] Current antithrombotic statements are conflicting for the need for posthospital discharge thromboprophylaxis in hospitalized COVID-19 patients, with some advocating for no routine thromboprophylaxis. In contrast, others advocate for the use of extended thromboprophylaxis in high-risk groups.[13-15]

Considering the in-hospital venous thromboembolism (VTE) burden of COVID-19 and previous data on medically ill patients showing that more than half of the VTE events occur after hospital discharge,[16] it is reasonable to question the potential role of extended VTE and arterial thromboembolism (ATE) prophylaxis in the posthospital discharge setting for these patients. In this trial, we aim to evaluate the safety and efficacy of rivaroxaban 10 mg once daily for 35 ± 4 days versus no intervention after hospital discharge in COVID-19 patients who were at increased risk for VTE and ATE and have received parenteral VTE prophylaxis during hospitalization.

Trial rationale

After hospitalization for medical illness, extended postdischarge thromboprophylaxis is a paradigm with recent evidence not incorporated in the latest guidelines.

The Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing PostDischarge Venous Thrombo-Embolism Risk trial (MARINER trial) evaluated rivaroxaban 10 mg or 7.5 mg once daily (when creatinine clearance < 50 mL/min) vs placebo for 45 days after hospital discharge, in 12,019 medically ill patients.[17] Patients were considered for the trial if they had elevated thrombotic risk according to the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk score[19] combined to D-Dimer results (IMPROVE ≥ 4 or IMPROVE = 2 or 3 and a plasma d-dimer level of more than twice the upper limit of the normal range). Patients with high bleed risk, defined as any of the following: active cancer, dual antiplatelet therapy, bronchiectasis/ pulmonary cavitation, gastroduodenal ulcer or bleeding within the previous 3 months before randomization, were not included in the MARINER trial. Although the trial failed to achieve the primary endpoint of symptomatic VTE or VTE related death (0.83% vs 1.1%; HR 0.76, 95% CI: 0.52-1.09), there was a significant 56% reduction in the relative risk of isolated symptomatic VTE, and a 27% relative risk reduction of symptomatic VTE and all-cause death. There was no significant increase in the major bleeding rate: 0.28% vs 0.15% (HR 1.88; 95% CI: 0.84-4.23).[17]

Although COVID-19 was not represented in previous trials on VTE prevention, acute infectious diseases and respiratory failure were prevalent, so it is reasonable to expect at least a similar benefit from extended thromboprophylaxis in COVID-19 patients. Moreover, considering the usually prolonged hospital admissions and long-lasting immobility during COVID-19 treatment, high prevalence of the underlying cardiovascular disease, and obesity, we estimated that the IMPROVE VTE risk score would be high in a significant proportion of hospitalized COVID-19 patients.

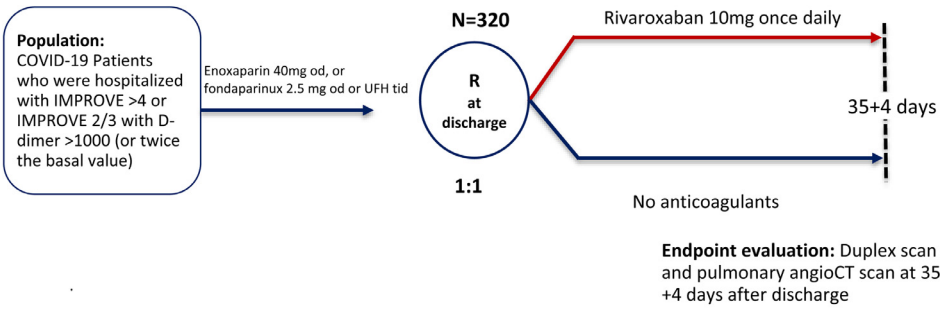
Recent data suggest that this strategy also reduces arterial events. In a prespecified analysis of the MARINER trial, the composite efficacy endpoint (symptomatic VTE, myocardial infarction, nonhemorrhagic stroke, and cardiovascular death) was reduced by 28% without significantly increasing major bleeding with the 10 mg dose of rivaroxaban.[18]

Given that extended VTE prophylaxis postdischarge significantly reduces thrombotic events, including VTE related-death and ATE with acceptable bleeding rates in selected patients, we have decided to evaluate such a strategy in COVID-19 patients. We have chosen rivaroxaban 10 mg orally up to 35 ± 4 based on its availability, the MARINER trial results (with 56% reduction of symptomatic VTE and a 28% reduction in major thromboembolism) the setting of postdischarge with in-hospital VTE prophylaxis with parenteral agents.

Study design

The Brazilian National Commission for Research Ethics and ethics committees at the participating sites have approved the MICHELLE trial (Medically Ill hospitalized Patients for Covid - THrombosis Extended ProphyLaxis with rivaroxaban ThErapy). It is a prospective, randomized, multicenter (14 sites in Brazil), open-label trial designed to test the efficacy and safety of extended thromboprophylaxis of rivaroxaban for 35 ± 4 days *versus* no pharmacologic intervention after hospital discharge in COVID-19 patients who were at increased risk for VTE and ATE and have received parenteral VTE prophylaxis during hospitalization. Patients will be assigned at hospital discharge to either once daily rivaroxaban at a dose of 10 mg once daily or regular follow-up for 35 ± 4 days, without extended anticoagulation (**Figure 1**).

Figure 1



Efficacy Endpoint: A composite of symptomatic VTE, VTE-related death or VTE detected at mandatory bilateral lower limbs venous duplex scan + pulmonary CT scan at day 35+4 and symptomatic arterial thromboembolism (myocardial infarction (MI), non-hemorrhagic stroke, major adverse limb events [MALE] and cardiovascular [CV] death in COVID-19 patients with moderate symptoms.

The MICHELLE Trial design. CTPA, computed tomography pulmonary angiogram; IMPROVED, modified International Medical Prevention Registry on Venous Thromboembolism; R, randomization; VTE, venous thromboembolism.

Table I. Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk score[19]

VTE risk factor	Points
Previous VTE	3
Known thrombophilia*	2
Lower-limb paralysis/ paresis	2
History of cancer**	2
Immobilization ≥1 day***	1
ICU/CCU stay	1
Age >60 years	1

CCU, cardiac care unit; ICU, intensive care unit; VTE, venous thromboembolism.

*A congenital or acquired condition leading to excess risk of thrombosis (eg, factor V Leiden, lupus anticoagulant, factor C or factor S deficiency);

** Cancer (excluding nonmelanoma skin cancer) present at any time in the past 5 years.

*** Immobilization is confined to bed or chair with or without bathroom privileges.

Both groups should have received prophylactic doses of enoxaparin (40 mg SC once daily), unfractionated heparin (UFH, 5.000 IU twice or 3 times a day), or fondaparinux (2.5 mg once daily) during the hospital stay. The study's primary objective is to determine the superiority of rivaroxaban versus no pharmacological intervention after discharge for hospitalization for COVID-19 infection. This is not a placebo-controlled study – the control arm receives no placebo medication. The study design is depicted in **Figure 1**. The IMPROVED VTE score is described in **Table I**. Inclusion and exclusion criteria are listed in **Table II**.

Visit schedule

Patients will be screened for the eligibility criteria during hospitalization and will be randomized after providing informed consent. Medication will be provided at randomization and must be started within the first 24 hours after hospital discharge and maintained for 35 days, irrespective of the second evaluation day (**Figure 2**). At randomization, patients will be encouraged to report in the protocol evaluations or by extra-telephone calls any symptom suggestive of VTE or bleeding. In every consultation, the investigators will perform detailed surveillance about chest pain, dyspnea, peripheral edema, pain in the lower limbs, and bleeding signs.

The first evaluation will be on day 7 after randomization and can be either by telephone or at the outpatient clinic. The second evaluation will be on day 35 ± 4 at the outpatient clinic. On the same day, computed tomography pulmonary angiogram (CTPA) and lower limbs venous Duplex scan will be performed. The third and last protocol evaluation will be on day 75 ± 5, by telephone call or at the outpatient clinic (Figure 2).

Primary Outcome: A composite of symptomatic VTE, VTE-related death, and asymptomatic VTE detected by bilateral lower limbs venous duplex scan and computed tomography pulmonary angiogram and symptomatic ATE (myocardial infarction [MI], nonhemorrhagic stroke, major adverse limb event [MALE], and cardiovascular [CV] death at day 35).

Key safety outcome

Incidence of major bleeding according to ISTH criteria: a major bleeding event according to ISTH is defined as evident hemorrhage associated with a decrease in hemoglobin levels of 2 g/dL or higher or leading to transfusion of 2 or more units of red blood concentrate or whole blood, or hemorrhage occurring in a critical site: eg, intracranial, intraspinal, intraocular, pericardial, intra-

Table II. Inclusion and exclusion criteria

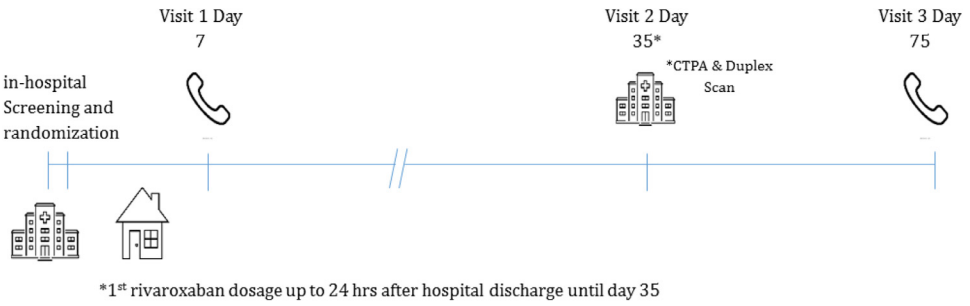
Inclusion criteria
Male and nonpregnant female patients 18 years of age or older
Positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for SARS-CoV-2 in a respiratory tract sample
Pneumonia confirmed by chest imaging
Additional risk factors for VTE, as indicated by a total modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk score of 4 or higher (scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism; minimal clinically important difference, 2) or a risk score of 2 or 3 plus a plasma d-dimer level of more than twice the upper limit of the normal range at the time of discharge (Table I).
Both groups should have received prophylactic doses of enoxaparin (40 mg SC once-daily), fondaparinux (2.5 mg once daily), or unfractionated heparin (UFH, 5.000 IU twice or 3 times a day), during the hospital stay
Exclusion criteria
Age <18 years
Physician decision that involvement in the trial was not in the patient's best interest
Any hemorrhage (defined as hemorrhage requiring hospitalization, transfusion, surgical intervention, invasive procedures, occurring in an anatomically critical site, or causing disability) within three months before randomization or occurring during the initial hospitalization period.
Major surgery, parenchymal organ biopsy, ophthalmic surgery (excluding cataract surgery) or serious trauma (including head trauma) within four weeks prior to randomization. The investigators criterion should be applied, but the following guidelines can be considered for the purpose of this study: Major surgeries often involve opening one or more major body cavities: the abdomen, chest, or skull, and can stress vital organs. Major surgeries are usually performed using general anesthesia in a hospital operating room by a surgeon (or surgeons) and usually require admission for at least one night in the hospital after surgery. On the other hand, with minor surgeries, the main body cavities are not opened. Minor surgeries may involve the use of local, regional, or general anesthesia and can be performed in the emergency room, in an outpatient operating room, or in a clinical office. Vital organs are usually not stressed, and surgery can be performed by a single doctor, who may or may not be a surgeon. In general, the person can return home on the same day that minor surgery is performed. The investigators criteria should be applied, but fracture or concussion should be considered serious head trauma, although external trauma without fracture or concussion may be considered for inclusion.
Any major planned surgery (see exclusion criterion #2) or important invasive diagnostic procedure provided for during the clinical study.
Participants with any known coagulopathy or hemorrhagic diathesis or an international normalized ratio (INR) > 1.5 during initial hospitalization without a subsequent value (the last value before randomization) that is 1.5.
A history of hemorrhagic stroke or any intracranial hemorrhage at any time in the past, evidence of primary intracranial hemorrhage on CT or MRI imaging of the brain, or clinical presentation consistent with intracranial hemorrhage. This also applies to participants hospitalized due to ischemic stroke at randomization. Participants with hemorrhagic transformation of an ischemic infarction prior to randomization are not excluded unless there is evidence of parenchyma hemorrhage (types HP-1 and HP-2): Hemorrhagic infarction type 1 (IH-1) is defined as a small petechiae along the margins of the infarction and type 2 IH (IH-2) is defined as more confluent petechiae within the infarcted area, but without expansive effect. HP type 1 (HP-1) is defined as hematoma in 30% of the infarct area with some mild expansive effect; HP type 2 (HP-2) is defined as dense hematoma > 30% of the infarction area with substantial expansive effect or as any hemorrhagic lesion outside the infarction area (Berger, 20012). Participants with type 1 and IH-2 hemorrhagic infarction are NOT excluded from this study, but participants with HP-1 and HP-2 are excluded from this study.
The participant has a history or presence of intracranial neoplasia (benign or malignant), brain metastases, arteriovenous malformation (VA) or aneurysm.
Active gastroduodenal ulcer, defined as diagnosed at three months, or current known or symptomatic arteriovenous malformations of the gastrointestinal tract.
Platelet count in the screening < 50 x 109 cells/l.
Active cancer (excluding non-melanoma skin cancer), defined as cancer that is not in remission or requires active chemotherapy or auxiliary therapies such as immunotherapy or radiotherapy. Chronic hormone therapy (e.g., tamoxifen, anastrozole, leuprolide acetate) is allowed for cancer in remission.
Any clinical picture (e.g., atrial fibrillation) requiring the use of any parenteral(s) or oral anticoagulant(s) (e.g., sodic warfarin or vitamin K antagonists, factor II inhibitors or Xa, fibrinolytics) concomitantly with the study drug.
Bilateral and unilateral amputation of the lower extremities above the knee.
Participant presenting allergy, hyper or known intolerance to rivaroxaban or any of its excipients.
Severe renal failure (baseline CrCl < 30 ml/min calculated using the Cockcroft-Gault)
Known significant liver disease (e.g., acute hepatitis, active chronic hepatitis, cirrhosis) that is associated with coagulopathy or moderate or severe hepatic impairment.
Known HIV infection.

articular, intramuscular with compartmental, retroperitoneal syndrome, or a fatal outcome.

Clinically relevant nonsignificant bleeding is defined as an evident hemorrhage not meeting the criteria of significant bleeding but associated with medical intervention, unscheduled contact (visit or phone call) with a doctor, interruption (temporary) of study treatment, or associated with discomfort to the participant such as pain or impairment of daily activities.

Another bleeding is defined as any other evident hemorrhage that does not meet the ISTH criteria for significant or nonsignificant clinically relevant hemorrhage.[19]

Figure 2



The MICHELLE Trial visit schedule. CTPA, computed tomography pulmonary angiogram.

Secondary outcomes

Secondary Efficacy Outcomes Secondary endpoints are to compare rivaroxaban with standard post-hospital discharge treatment in clinically ill patients at high risk for VTE:

- VTE-related death (death by PE or death in which PE cannot be excluded as the cause) and symptomatic VTE (DVT of the lower extremities and non-fatal PE).
- The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and all-cause mortality.
- The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE), myocardial infarction (IM), non-hemorrhagic stroke and cardiovascular death (CV) (death from known CV and death in which the CV cause cannot be excluded; by this definition, a VTE-related death is considered a CV death).

A composite of MI, stroke, arrhythmias, heart failure, VTE, and all-cause death, and a combination of major and clinically relevant nonmajor bleeding and all bleeding.

Sample size

The sample size was calculated assuming the power of 80%, a significance level of 0.05, the response anticipated for the occurrence of the primary efficacy endpoint of 15% in the standard of care arm (control group) and 5% of the treatment group, with a relative risk reduction of 66.67%. In the MARINER trial[17], the relative risk reduction was 56% for symptomatic VTE events, and on the meta-analysis of the 4 extension trials, the relative risk reduction was 40% to 50%.[20] Given that COVID-19 is a more thrombogenic disease, and we will for first-time computed tomography pulmonary angiogram scans for the primary endpoint, we believe that a relative risk reduction of around 66% is realistic for both venous and arterial events. If there is a true difference in favor of the proposed treatment of 10% (15% vs 5%), then 282 patients are required with a power of 80% that the upper limit of 95% confidence interval will exclude a difference in favor of the standard group of more than 50%. With a drop-out rate of 10%, a total of 320 patients will be necessary (160 per arm).

Beyond the initial sample size calculation, a formal interim analysis by the Data and Safety Monitoring Board (DSMB) evaluating primarily safety may recommend modifications in the sample size. The first formal interim analysis was performed when the first 200 patients have been enrolled and have completed the 35-day follow-up visit. As of now, July 2021, all 320 targeted patients have been enrolled.

Statistical analysis

For the efficacy analysis, the cumulative incidence of the composite of events will be compared between the rivaroxaban and control group, and the relative risk (RR) or risk ratio will be estimated. The superiority of the treatment is claimed if the upper limit of 95% confidence interval is less than one.

For the safety analysis, statistical tests will be 2-sided, with a type I error rate of 5% and a 95% confidence interval. The details of the statistical analysis will be described in the study's statistical analysis plan (SAP).

Trial leadership

The study was designed and led by an Executive/Steering Committee composed of academic investigators from the centers involved with the study and other experienced clinical researchers in this field. The data monitoring committee will oversee the data and safety of the study. All primary efficacy and principal safety events will be centrally and independently adjudicated.

Data and Safety Monitoring Board and Clinical Events Committee

An independent DSMB will monitor safety data on an ongoing basis with access to unblinded data. The DSMB has reviewed the results from a formal interim analysis once 200 patients have completed the study. The DSMB will use a *P*-value <.001 in the interim analysis to declare an overwhelming statistically significant difference in outcomes between study groups to guide their recommendations. An overall *P*-value <.05 will be used to declare statistical significance at the end of the study. A detailed DMSB charter provided stopping rules for the trial for efficacy and safety issues. There will be no interruption for futility.

The Clinical Events Committee (CEC) is composed of medical experts eligible by the board or certified by the board as appropriate and necessary. Committee members do not directly include study participants, are not involved in monitoring the MICHELLE study, and have no direct operational responsibilities for conducting the study. Members will analyze all suspected outcome events as described below that occurred after randomization as soon as they become available and evaluate and classify consistently and impartially, according to the definitions in the clinical events chart, remaining blind to treatment assignment.

Clinical events definitions

•Death: VTE-related: death due to confirmed PE documented by objective testing or autopsy. VTE-related death cannot be ruled out: attributed to a documented cause, and PE cannot be ruled out (unexplained death). Other: defined as death not included in the above categories. All-cause death: all the deaths that occur in the study population, regardless of the cause. Cardiovascular death: death resulting from an acute MI, sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV conditions. Limb arterial thromboembolism: Acute limb ischemia, defined as a sudden worsening of limb perfusion requiring hospitalization and new pulse deficit with associated rest pain, pallor, paresthesia, or paralysis, and either confirmation of arterial obstruction (imaging, hemodynamics, intraprocedural findings, pathologic evaluation) or treatment with thrombolysis, thrombectomy, or urgent revascularization.

Myocardial infarction: Clinical evidence of acute myocardial ischemia, with detection of a rise and/or fall of troponin values with at least one value above the 99th percentile URL and at least one of the following: symptoms of myocardial ischemia; new ischemic changes in electrocardiogram; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; identification of a coronary thrombus by angiography.[21]

Stroke: Sudden numbness or weakness in the face, arm, or leg, especially on one side of the body. Sudden confusion, trouble speaking, or difficulty understanding speech. Sudden trouble seeing in one or both eyes. Sudden trouble walking, dizziness, loss of balance, or lack of coordination. Confirmed by cerebral CT scans or magnetic resonance imaging (MRI).

DVT: Demonstration of one or more of the following diagnostic criteria: a noncompressible venous segment on compression ultrasound of the deep-venous system or in patients with a previous history of DVT, a new noncompressible venous segment or a substantial increase (4 mm or more) in the diameter of the vein during total compression in a previously abnormal segment on ultrasound. Or the presence of an intraluminal filling defect in the venography.

PE: The anatomical extent of PE will be classified by the evaluation committee as segmental or greater or subsegmental. The totality of clinical, imaging, and laboratory findings should be considered. Demonstration of one or more of the following diagnostic criteria: A defect in the intraluminal filling in computed tomography (CT) or spiral CT angiography. A defect in the intraluminal filling in a pulmonary angiography or cut in a vessel with a diameter greater than 2.5 mm; or a pulmonary perfusion test of at least 75% of a segment with corresponding normal ventilation (high probability ventilation-perfusion test [V-Q]; An abnormality in a V-Q exam without high probability associated with DVT documented by ultrasound or venography. In the absence of an imaging test in a hemodynamically unstable patient, evidence of right ventricular dysfunction by a transthoracic or transesophageal echocardiogram (European Society of Cardiology [ESC] criteria).

The Michelle trial IRB number is CAAE 35432520.3.1001.5485 and is registered at www.clinicaltrials.gov (NCT04662684).

Discussion

Extended VTE prophylaxis after hospitalization for medically ill patients remains controversial. Despite the results of the MARINER trial[17] that did not show a significant difference in reducing VTE-related death after 45 days postdischarge of rivaroxaban versus placebo, this strategy reduced by 56% the rate of symptomatic VTE with no increase of major bleeding. Given the high prothrombotic nature of the COVID-19 pandemic, in addition to a fair number of patients leaving the hospital with a high IMPROVE VTE score and D-dimer levels, it is reasonable to assess the role of a prolonged VTE prophylaxis strategy in reducing thrombotic events in hospitalized COVID-19 patients without significantly increasing major bleeding. Recent prospective registry in the US showed

a 7.13% rate of VTE/ATE/ all-cause mortality (ACM) and a 46% RRR using postdischarge anticoagulants majority of patients taking rivaroxaban 10 mg once daily[10], but data from prospective randomized controlled trials are still warranted.

Other clinical studies are actively assessing extended thromboprophylaxis in COVID patients. A study in Mexico enrolling 130 patients evaluates prophylactic and full-dose heparin in hospital followed by rivaroxaban 10 mg once daily or no intervention (NCT04508439). The out-of-hospital phase will evaluate adverse events and biomarkers. Another study, the XACT Trial (NCT04640181), is evaluating 150 patients randomized to either in-hospital enoxaparin or oral rivaroxaban while hospitalized and through discharge for a total of 28 days. This trial evaluates different rivaroxaban doses (10, 15, and 20 mg once-daily) with the primary endpoint a combination of death or 30-day all-cause mortality, mechanical ventilation, intubation, and transfer to an intensive care unit (ICU).

A larger trial, the ACTIV-4c adaptative convalescent protocol (NCT04650087) in the US, investigates in planned 4,000 patients the effectiveness and safety of anticoagulants and antiplatelets (apixaban, aspirin, or placebo) administered to patients who have been discharged from the hospital. The primary objective is reducing MI, stroke, arterial and venous thrombosis, and death within 30 days after hospital discharge for moderate and severe COVID-19. In the MICHELLE trial, the study drug is rivaroxaban 10 mg once daily compared to no intervention with the novelty of an evaluation (pulmonary computed tomography scans for the first time and lower limb Doppler ultrasound) in a relatively shorter timeframe on day 35, instead of day 45 like the MARINER Trial and ACTIVE-4c.

The MICHELLE trial is part of a comprehensive program on anticoagulation strategies for Brazil's COVID-19 pandemic. Four other randomized clinical trials are evaluating other essential knowledge gaps. The COALIZAO-ACTION trial showed that in patients hospitalized with COVID-19 and elevated D-dimer concentration, in-hospital therapeutic anticoagulation with rivaroxaban 20 mg once-daily followed by rivaroxaban 20 mg once-daily up for 30 days did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation. The authors conclude that the rivaroxaban 20 mg once-daily dose should be avoided as a routine anticoagulation strategy for this population.[22] The CARE trial (NCT0475785) is enrolling 1,000 COVID-19 outpatients with moderate symptoms to either rivaroxaban 10 mg versus placebo to reduce the need for hospitalization and mortality. The APOLLO trial (NCT04746339) evaluates apixaban 2.5 mg BID versus placebo in the out-of-hospital setting to reduce mortality. All these 4 trials together provide essential information about the management of COVID-19 patients in the prehospital, in-hospital and, postdischarge settings and should help physicians in the decision-making process around this infection.

One potential limitation of the MICHELLE trial is its sample size. We are assuming a considerable relative risk reduction of 66% of events on the active arm. However, we are using pulmonary angio-CT scan combined with lower limbs Doppler ultrasound on day 35 + 4 and a combination of venous and arterial events. Such a strategy might detect a significant number of asymptomatic events. Recent data consistently show that asymptomatic proximal DVT found by screening ultrasonography is strongly associated with increased mortality in hospitalized medical patients.[23] Such remains a relevant endpoint in trials of thromboprophylaxis for this patient population.[24]

Conclusion

The MICHELLE trial results will provide high-quality evidence around the role of extended posthospital discharge thromboprophylaxis in hospitalized COVID-19 patients and will help guide medical decisions in clinical practice.

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Declaration of interest

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