TITLE

Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration

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SHORT TITLE

Anticoagulation Trials in COVID-19

KEY WORDS

Anticoagulant, COVID-19, Pulmonary Embolism, Research Networks, Thrombosis

ESSENTIALS

- Patients with COVID-19 coagulopathy are at a high risk of thrombosis and death.
- This review summarizes ongoing trials evaluating anticoagulant interventions in COVID-19.
- A total of 20 randomized trials evaluate different dose regimens of anticoagulant interventions.
- Global collaboration may help to complete trials faster to get answers that will save lives.

ABSTRACT

Introduction: Coronavirus disease (COVID-19) is associated with a high incidence of thrombosis and mortality despite standard anticoagulant thromboprophylaxis. There is equipoise regarding the optimal dose of anticoagulant intervention in hospitalized patients with COVID-19 and consequently, immediate answers from high-quality randomized trials are needed.

Methods: The World Health Organization's International Clinical Trials Registry Platform was searched on June 17, 2020 for randomized controlled trials comparing increased dose to standard dose anticoagulant interventions in hospitalized COVID-19 patients. Two authors independently screened the full records for eligibility and extracted data in duplicate.

Results: A total of 20 trials were included in the review. All trials are open-label, 5 trials use an adaptive design, 1 trial uses a factorial design, 2 trials combine multi-arm parallel group and factorial designs in flexible platform trials, and at least 15 trials have multiple study sites. With individual target sample sizes ranging from 30 to 3,000 participants, the pooled sample size of all included trials is 12,568 participants. Two trials include only ICU patients, and 10 trials base patient eligibility on elevated D-dimer levels. Therapeutic intensity anticoagulation is evaluated in 14 trials. All-cause mortality is part of the primary outcome in 14 trials.

Discussion: Several trials evaluate different dose regimens of anticoagulant interventions in hospitalized patients with COVID-19. Since these trials compete for sites and study participants, a collaborative effort is needed to complete trials faster, conduct pooled analyses and bring effective interventions to patients more quickly.

INTRODUCTION

Several observational studies indicate that coronavirus disease (COVID-19) is associated with a high incidence of venous thromboembolism (VTE) or arterial thrombosis despite standard anticoagulant thromboprophylaxis.[1,2] The risk of thrombotic complications is particularly high in patients admitted to the intensive care unit (ICU) [1,2]. Thromboinflammation is also involved in disease progression in that thrombi in pulmonary arteries and alveolar capillary microthrombi were found in the majority of deceased COVID-19 patients in recent autopsy studies.[3-5] Such microthrombi may form as consequence of endothelial injury, caused by effects of intraepithelial virus and perivascular inflammation,[5,6] and diffuse alveolar damage which may disrupt the balance between fibrinolysis and coagulation.[4] These autopsy findings further reinforce the important role of COVID-19-induced coagulopathy and venous or arterial thrombi as potential immediate cause of death in patients with COVID-19.[3,4] Anticoagulant interventions at increased doses may mitigate this risk of thrombosis and mortality. A single-center retrospective cohort study suggested that therapeutic dose anticoagulation was associated with a lower in-hospital mortality in 395 mechanically ventilated patients,[7] but interpretation of the study is hampered by its observational nature and associated biases.[8] A propensity score matched analysis of 139 patients who were on therapeutic anticoagulation prior to diagnosis of COVID-19 and 417 patients who were not on anticoagulation prior to diagnosis showed no difference in mortality or requirement for mechanical ventilation between the two groups.[9] Elevated D-dimer levels on hospital admission are associated with an increased risk of VTE, bleeding and mortality in COVID-19 patients.[10-12] Whether management based on risk stratification using D-dimers improves the risk-benefit ratio of increased dose anticoagulant interventions remains unclear.

Because therapeutic intensity anticoagulation is associated with an increased risk of bleeding,[13] the mere increase in risk of thrombotic events does not justify in itself therapeutic anticoagulation in patients with COVID-19. Published guidance documents based on expert opinion in the absence of completed trials are available.[1,14-23] These differ in their recommendations, as some suggest anticoagulants at prophylactic

dose in patients with COVID-19 while awaiting more definitive data from ongoing randomized controlled trials,[1,14-19] and others suggest anticoagulants at intermediate or therapeutic doses in high-risk patients with COVID-19.[20-23] Despite these differences, experts agree on the urgent need for high-quality data from adequately powered randomized controlled trials to guide the optimal dose of anticoagulation in patients with COVID-19.

In response to the urgent need for studies evaluating efficacy and safety of interventions for COVID-19 patients, clinical studies have been designed, registered and funded at an unprecedented rate. As of June 17, 2020, the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) includes 3,591 study protocols related to COVID-19. Several studies have not yet started enrolling or have enrolled only a few participants. Trials which aim to answer a similar question or evaluate interventions in the same population may compete for eligible patients and study sites. This can lead to delays in trial completion or even failure to accrue the required sample size.[24] Therefore, collaborative efforts, such as an individual patient data meta-analysis, merging two or more trials into one or opening new study sites in regions with rising COVID-19 rates, may become necessary to answer the most pressing questions related to the clinical management of patients with COVID-19.

The objective of this scoping review, led by members of the International Network of VENous Thromboembolism Clinical Research Networks (INVENT-VTE; www.INVENT-VTE.com), was to map and describe planned or ongoing randomized controlled trials that compare different anticoagulant dosing strategies in patients with COVID-19. This review provides a basis for an international collaboration to reduce duplication of efforts and is a call to action to researchers to combine individual patient data across similar trials and to assess the efficacy and safety of interventions across key subgroups of patients.

METHODS

Reporting of this study adheres to the PRISMA statement items on scoping reviews.[25] The study protocol was registered with the University of Ottawa's digital repository of research (available at hdl.handle.net/10393/40584). Combining terms for 'COVID', 'COVID-19', 'coronavirus', 'SARS-CoV-2', 'severe acute respiratory syndrome 2' and 'venous thromboembolism', 'deep vein thrombosis', 'pulmonary embolism', 'thromboprophylaxis', 'anticoagulation', 'heparin', 'Liquemin', 'low-molecular-weight heparin', 'enoxaparin', 'Clexane', 'Lovenox', 'dalteparin', 'Fragmin', 'tinzaparin', 'Innohep', 'nadroparin', 'Fraxiparin', 'fondaparinux' or 'Arixtra', we searched the WHO ICTRP for protocols of randomized controlled trials comparing different dosing regimens of anticoagulant interventions in adult patients hospitalized with COVID-19. Trials including only ambulatory patients or comparing anticoagulant or antiplatelet interventions to placebo or no intervention were not eligible. The WHO ICTRP is a meta-register which includes records from 18 clinical trials registries across the globe (www.who.int/ictrp). The database was searched from inception to June 17, 2020, which is 2 days after an update of records from individual registries. Content experts were consulted to identify additional studies. Using Microsoft Excel, two authors independently screened the full records for eligibility and extracted data of included trials in duplicate. Disagreements were resolved by discussion to reach consensus or by involving a third reviewer if needed. Trial characteristics were analyzed using descriptive statistics. We invited the principal investigators of identified trials to take part in this call to action and provide additional information on their respective trials where appropriate.

RESULTS and DISCUSSION

A total of 61 records were screened for eligibility; 60 studies were identified through the database search and 1 additional study was identified by content experts. After exclusion of 41 records due to wrong study design (n=30), wrong intervention (n=9) or duplicate registration (n=2), 20 trials were included (Table 1). There was disagreement between the two authors who extracted data for a total of 11 cells in table

1 and 2. All disagreements were resolved by discussion. All trials are open-label; 5 trials use an adaptive design (i.e., a study design that "uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial"[26]); 1 trial uses a factorial design; 2 trials use multifactorial designs (i.e., evaluating 2 or more interventions in flexible platform trials combining multi-arm parallel group and factorial designs); and at least 15 trials have multiple study sites. Target sample sizes range from 30 to 3,000 participants, and when considering all but one trial which does not provide a sample size, the pooled target sample size is 12,568 participants. Two trials include only ICU patients, and 10 trials link patient eligibility to elevated D-dimer levels (Table 2). Therapeutic intensity anticoagulation with low-molecular-weight heparin, unfractionated heparin or rivaroxaban is evaluated in 14 studies, and 5 studies compare intermediate dose low-molecular-weight heparin (e.g., enoxaparin 40 mg twice daily) or prophylactic dose rivaroxaban to standard prophylactic dose heparin. Most trials use composite primary outcomes (Table 2). All-cause mortality is part of the primary outcome in 14 trials, invasive mechanical ventilation in 8 trials, VTE in 10 trials, and arterial thrombosis in 8 trials. Combinations of components of primary outcomes across studies are depicted in Figure 1. Estimated study completion dates range from September 2020 to June 2021.

In this scoping review, we identified 20 ongoing trials evaluating anticoagulant interventions in hospitalized patients with COVID-19 across 4 continents and 21 countries. The extraordinary effort to develop these important trials in such a short time and under unprecedented circumstances is commendable. This swift development was driven by the urgency to find efficacious and safe interventions for patients with COVID-19. Speedy completion of these trials is crucial to provide the best care for patients with COVID-19. Many centers have already adapted their anticoagulant protocols for COVID-19[27] based on low-quality evidence while awaiting results of randomized controlled trials, placing these trials in jeopardy due to loss of equipoise. Ongoing measures to mitigate the pandemic will lead to a decrease in the daily number of new COVID-19 cases. As a consequence, enrollment of patients may slow down or stop in some regions in the near future which may affect the ability to complete these important

trials. In this situation, designs that afford rapid opening of study sites in regions with increasing infection rates will be required.

Findings here suggest that the COVID-19 research landscape is fragmented and rapidly changing. Researchers are developing study protocols quickly and often implementing them first on a local level. While an urgent need for answers opens opportunities for funding and fast-track study approval by ethics committees or regulatory agencies, it may lead to duplication of efforts and conduct of trials that may never be completed due to poor recruitment or were underpowered to begin with. In an analysis of UK government-funded trials prior to COVID-19, 45% did not reach 80% of the pre-specified sample size and only 31% reached the intended sample size in their proposed time frame.[28] Sample size calculations can often include back and forth dance between a feasible target sample size and the desired effect size [29]. This "sample size samba"[29] allows researchers to achieve satisfactory power but can lead to inflation of the minimal clinically important difference of the primary outcome. Nonetheless, methodologically strong small studies have value,[29] because they can be combined in a meta-analysis which may achieve convincingly conclusive results.[30]

The need to globally coordinate research efforts existed prior to COVID-19, but the fast pace, fragmentation and high-pressure state on COVID-19 research efforts has triggered the need for urgent international collaboration and future innovative solutions to solve this problem. It also highlights the need to strengthen inter-disciplinary networks and collaboration since study objectives and primary outcomes may vary despite studying similar interventions in the same populations. Engagement of every specialty involved in the care of patients with COVID-19 may be key to design and successfully conduct meaningful trials. Furthermore, this scoping review also accentuates the need for standardization of key data elements across trials, such as Common Data Elements (http://isth.breakthrough.healthcare)[31] and related Core Outcome Sets to capture outcomes in a purposeful and standardized way.

A shift in research culture from one of competition to genuine collaboration is needed. We call for action to establish an international collaboration of principal investigators of these ongoing trials who are willing to share individual patient data prior

to study completion if they will not meet recruitment targets in the coming months, or share a minimal outcome dataset in real-time regardless of achieving a target sample size in order to obtain early results in a timely manner. The latter may include a shared Data and Safety Monitoring Board which evaluates efficacy and safety using pooled interim results. This would also allow to halt trials if interim results show a clear and consistent benefit or harm. Joining forces may not only enable that evidence can be rapidly delivered to the bedside, but also permits the global community to focus on the next potential solution (e.g., trials evaluating combined anti-platelet/anticoagulant strategies, factor-XIa inhibitors) and evaluate important patient subgroups.

We propose an international collaboration of anticoagulation trials in COVID-19 which will be supported by INVENT-VTE (www.INVENT-VTE.com) - an academic, non-for-profit network of national VTE networks from Australia and New Zealand, Canada, France, Ireland, the Netherlands, Germany, Italy, Norway, and the United States. We are dedicated to the concept of global collaboration to conduct and complete trials better and faster, thus reducing costs and research waste. By working together, we may determine the optimal anticoagulation strategy in patients with COVID-19.

AUTHOR CONTRIBUTIONS

TT, MEM, MR, and GLG contributed to concept and design of the study. TT and MEM selected studies and extracted data. TT, MEM, LS, MR, and GLG drafted the initial manuscript. All authors revised the manuscript critically and approved the final version.

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Table 1. Registration details (as of June 17, 2020) and study characteristics of trials evaluating anticoagulant interventions in hospitalized patients with COVID-19

Study Acronym or PI	Trial ID	Source registry	Countries	Date of registration	Estimated study completion date
COVID-HEP	NCT04345848	ClinicalTrials.gov	Switzerland	07/04/2020	March 2021
CORIMMUNO-COAG	NCT04344756	ClinicalTrials.gov	France	09/04/2020	September 2020
RAPID COVID COAG	NCT04362085	ClinicalTrials.gov	Canada, Ireland, Saudi Arabia, United States	20/04/2020	December 2020
HeSAcovid	RBR-949z6v	REBEC	Brazil	06/05/2020	July 2020
COALIZAO ACTION	NCT04394377	ClinicalTrials.gov	Brazil	08/05/2020	December 2020
COVID PACT	NCT04409834	ClinicalTrials.gov	United States	28/05/2020	May 2021
Berger et al.	NCT04359277	ClinicalTrials.gov	United States	20/04/2020	April 2021
REMAP-CAP	NCT02735707	ClinicalTrials.gov	Australia, Belgium, Canada, Croatia, France, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Saudi Arabia, Spain, United Kingdom, United States	20/04/2020[2]	December 2021
ATTACC	NCT04372589	ClinicalTrials.gov	Brazil, Canada, Mexico, United States	24/04/2020	January 2021
Albaghdadi et al.	NCT04377997	ClinicalTrials.gov	United States	01/05/2020	January 2021
HEP-COVID	NCT04401293	ClinicalTrials.gov	United States	20/05/2020	April 2021
IMPACT	NCT04406389	ClinicalTrials.gov	United States	26/05/2020	June 2021
COVID-19 HD	NCT04408235	ClinicalTrials.gov	Italy	26/05/2020	June 2021
COVI-DOSE	NCT04373707	ClinicalTrials.gov	France	01/05/2020	October 2020[1]
X-Covid 19	NCT04366960	ClinicalTrials.gov	Italy	24/04/2020	November 2020
Heparin-SARS-CoV2	EUCTR2020-001891-14-ES	EU Clinical Trials Register	Spain	05/05/2020	Not provided
Perepu et al.	NCT04360824	ClinicalTrials.gov	United States	13/04/2020	April 2021
IMPROVE-COVID	NCT04367831	ClinicalTrials.gov	United States	27/04/2020	April 2021
COVID-PREVENT	NCT04416048	ClinicalTrials.gov	Germany	02/06/2020	May 2021
ACOVACT	NCT04351724	ClinicalTrials.gov	Austria	10/04/2020	December 2020

Abbreviations: IPD, individual patient data; PI, principal investigator.

[1] Estimated study completion date has been extended.

[2] Date of approval of the first version of the COVID-19 appendix to the REMAP-CAP protocol.

Table 2. Study design, population and intervention of trials evaluating anticoagulant interventions in hospitalized patients with COVID-19, as per information provided by principal investigators and at WHO ICTRP (accessed on July 17, 2020)

Study Acronym or PI	Study design	Target sample size	Population[1]	Intervention	Control	Primary outcome (time frame)
COVID-HEP	Randomized, open-label, multicenter, clinical trial	200	1) Non-ICU patients with D-dimer >1000 μg/L or 2) ICU patients	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH (augmented dose for ICU patients)	Composite outcome of arterial or venous thrombosis, DIC and all-cause mortality (30 days)
CORIMMUNO-COAG	Randomized, open-label, multicenter, clinical trial	808	Non-ICU patients requiring oxygen (group 1) or ICU patients requiring mechanical ventilation (group 2)	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH	Group 1: survival without ventilation (14 days) or group 2: ventilator free survival (28 days)
RAPID COVID COAG	Randomized, open-label, adaptive, multicenter, clinical trial	462	Non-ICU patients with elevated D-dimer and not requiring ventilation	Therapeutic LMWH or UFH	Prophylactic LMWH, UFH or fondaparinux	Composite outcome of ICU admission, non-invasive positive pressure ventilation, invasive mechanical ventilation, or all-cause death (28 days)
HeSAcovid	Randomized, open-label, single-center, clinical trial	30	Patients with respiratory failure and D-dimer ≥1000 μg/L	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH	Comparison between before and after the PO2 / FIO2 ratio, days without mechanical ventilation (28 days)
COALIZAO ACTION	Randomized, open-label, multicenter, clinical trial	600	Non-ICU and ICU patients with D-dimer ≥3x ULN	Therapeutic rivaroxaban, LMWH or UFH	Prophylactic LMWH	Ordinal outcome including mortality, number of days alive, number of days in the hospital and number of days with oxygen therapy (30 days)
COVID PACT	Randomized, 2x2 factorial open-label, multicenter, clinical trial	750	ICU patients	Therapeutic LMWH or UFH ±clopidogrel	Prophylactic LMWH or UFH ±clopidogrel	Venous or arterial thrombotic events (28 days)
Berger et al.	Randomized, open-label, single-center clinical trial	1000	Patients with D-dimer 500-10,000 μg/L	Therapeutic LMWH or UFH	BMI- and weight-adjusted prophylactic dose LMWH	• All-cause mortality (1 year) • Incidence of cardiac arrest (21 days) • Incidence of symptomatic deep venous thrombosis (21 days) • Incidence of pulmonary embolism (21 days) • Incidence of arterial thromboembolism (21 days) • Incidence of myocardial infarction (21 days) • Incidence of hemodynamic shock (21 days)

REMAP-CAP (COVID sub-platform)	Randomized, embedded, multifactorial, adaptive, platform trial	Adaptive, no max. sample size provided	Non-ICU and ICU patients with suspected or confirmed COVID-19	Therapeutic LMWH or UFH	Local standard thromboprophylaxis	Days alive and outside ICU (21 days)
ATTACC	Randomized, open-label, multicenter, adaptive clinical trial	Adaptive, max. sample size 3000	Patients not receiving mechanical ventilation	Therapeutic LMWH or UFH	Local standard thromboprophylaxis	Ordinal outcome including no intubation, intubation or mortality (30 days)
Albaghdadi et al.	Randomized, open-label, multicenter, clinical trial	300	Non-ICU and ICU patients with D-dimer >1,500 μg/L without severe ARDS	Therapeutic LMWH or UFH	Local standard thromboprophylaxis	1) Composite efficacy endpoint of death, cardiac arrest, symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, or hemodynamic shock (12 weeks) 2) ISTH major bleeding (12 weeks)
HEP-COVID	Randomized, open-label, multicenter, clinical trial	308	Patients with D-dimer >4x ULN or SIC score ≥4 stratified by ICU vs non-ICU stay	Therapeutic LMWH	Prophylactic or intermediate dose LWMH or UFH	Composite outcome of arterial thromboembolic events, venous thromboembolic events and all-cause mortality (30 days)
IMPACT	Randomized, open-label, clinical trial	186	Non-ICU or ICU patients requiring supplemental oxygen and D-dimer >3x ULN	Therapeutic LMWH, UFH, fondaparinux or argatroban	Intermediate dose LMWH, UFH or fondaparinux	Mortality (30 days)
COVID-19 HD	Randomized, open-label, multicenter, clinical trial	300	Patients not receiving mechanical ventilation with severe pneumonia and D-dimer >4x ULN or SIC score >4	Subtherapeutic LMWH	Prophylactic LMWH	Composite outcome of mortality, acute myocardial infarction, symptomatic arterial or venous thromboembolism, and need for non-invasive or invasive mechanical ventilation (30 days)
COVI-DOSE	Randomized, open-label, multicenter, clinical trial	602	Non-ICU and ICU patients	Weight-based intermediate-dose LMWH	Prophylactic LMWH (augmented dose for ICU patients)	Venous thromboembolism (28 days)
X-Covid 19	Randomized, open-label, multicenter, clinical trial	2712	Non-ICU patients	Intermediate-dose LMWH	Prophylactic LMWH	Objectively confirmed venous thromboembolism (30 days)
Heparin-SARS-CoV2	Randomized, open-label, multicenter, clinical trial	140	Patients not receiving high-flow oxygen therapy or mechanical ventilation	Intermediate-dose LMWH	Prophylactic LMWH	Need for oxygen therapy escalation or invasive mechanical ventilation or mortality during admission (30 day)
Perepu et al.	Randomized, open-label, multicenter, clinical trial	170	Non-ICU and ICU patients with modified ISTH DIC score ≥3	Intermediate-dose LMWH	BMI-adjusted prophylactic dose LMWH	All-cause mortality (30 days)
IMPROVE-COVID	Cluster randomized, open-label, single-center, adaptive trial	100	ICU patients	Intermediate-dose LMWH or UFH	BMI- and weight-adjusted prophylactic dose LMWH	Clinically relevant venous or arterial thrombotic events in ICU (30 days)

COVID-PREVENT	Randomized, open-label, multicenter, clinical trial	400	Non-ICU and ICU patients with D-dimer >1.5x upper limit of age-adjusted normal or high-sensitive troponin T >2x ULN and known CV risk factor	Therapeutic rivaroxaban	Prophylactic LMWH or UFH	Composite outcome of venous or arterial thromboembolism, myocardial infarction, non-hemorrhagic stroke, mortality or progression to intubation and invasive ventilation (35 days)
ACOVACT	Randomized, multifactorial, adaptive, open-label, multicenter, platform trial	500	Non-ICU and ICU patients	Rivaroxaban 5 mg twice daily	Local standard thromboprophylaxis	Sustained improvement (>48h) of one point on the World Health Organization Scale (29 days)

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CV, cardiovascular; DIC, disseminated intravascular coagulation; ICU, intensive care unit; ISTH, International Society of Haemostasis and Thrombosis; LMWH, low-molecular-weight heparin; PI, principal investigator; PaO2 / FiO2 ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; UFH, unfractionated heparin; ULN, upper limit of normal; SIC, sepsis-induced coagulopathy.

[1] All patients require to be hospitalized and have confirmed COVID-19 if not specified otherwise.

Figure 1. Mortality and or VTE and or mechanical ventilation as part of the primary outcome in anticoagulation trials in COVID-19.