TITLE
Randomized controlled trials assessing different dose regimens for anticoagulant thromboprophylaxis in patients with COVID-19: protocol for a scoping review

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1. INTRODUCTION, RATIONALE, and OBJECTIVE

Several observational studies indicate that coronavirus disease (COVID-19) is associated with a high incidence of venous thromboembolism (VTE) despite anticoagulant thromboprophylaxis at prophylactic doses.[1-11] The risk of VTE is particularly high in patients admitted to the intensive care unit (ICU) which led to the hypothesis that those patients may benefit from thromboprophylaxis at therapeutic doses. A single-center retrospective cohort study suggests that anticoagulation was associated with a lower in-hospital mortality in 395 mechanically ventilated patients, but the study is hampered by several bias due to its observational nature.[12] Because therapeutic anticoagulation is associated with an increased risk of bleeding, the mere increase in risk of VTE does not justify in itself therapeutic anticoagulation for thromboprophylaxis in COVID-19 patients. Indeed, the evidence-based American College for Chest Physician guidelines suggest standard-dose anticoagulant thromboprophylaxis in COVID-19 patients but acknowledges that randomized controlled trials evaluating therapeutic dose thromboprophylaxis are urgently needed, in particular for patients at very high risk of VTE, such as ICU patients. Most expert panel reports support this recommendation,[13-18] while only few experts suggest routine thromboprophylaxis at therapeutic doses in high-risk patients with COVID-19.[19-21]

In response to the urgent need for studies evaluating the efficacy and safety of interventions for COVID-19 patients, clinical studies were designed, registered and funded at an unprecedented rate. As of May 15th, 2020, the World Health Organization’s International Clinical Trials Registry Platform (WHO ICTRP) includes 2,738 COVID-related study protocols. While new cases of COVID-19 fortunately decline in many countries, several studies have not yet started enrolling or have included only few patients. Because trials aiming to answer the same question or to assess interventions in the same population are competing with each other for patients, completion of studies may be delayed, and some studies may even fail to accrue the required sample size. Therefore, collaborative efforts, such as, individual patient data meta-analysis, may become necessary to receive answers to the most pressing questions related to the clinical management of patients with COVID-19. The objective of this scoping review is to map and describe planned or ongoing randomized controlled trials comparing increased dose anticoagulant thromboprophylaxis to standard dose prophylaxis. The review may help reduce duplication of efforts and could provide the basis for an international collaboration aiming to combine individual patient data in case recruitment of patients would be slow across competing...
trials and or in order to assess efficacy and safety of interventions across different subgroups of patients.

2. METHODS
This protocol was developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) Statement.[22] The protocol of this scoping review will be registered with the University of Ottawa’s digital repository of research. Reporting of the final publication will adhere to the PRISMA statement items on scoping reviews.[23]

2.1. Eligibility criteria
Randomized controlled trials comparing different dosing regimens of anticoagulant thromboprophylaxis in patients with COVID-19 will be eligible.

2.1.1. Participants
Adult hospitalized patients with COVID-19.

2.1.2. Intervention
Anticoagulant thromboprophylaxis at increased dose (i.e., intermediate or therapeutic dose)

2.1.3. Comparator
Standard-dose anticoagulant thromboprophylaxis or standard of care as defined by individual study protocol.

2.1.4. Outcome
Studies do not require to specify a certain outcome to be eligible for the review, but all outcomes will be extracted and reported in the review.

2.1.5. Study design
Studies eligible for this scoping review will be randomized controlled trials.

2.2. Search strategy
We will search the WHO ICTRP for relevant protocols combining terms for ‘randomized controlled trial’, ‘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’ and ‘arixtra’. The WHO ICTRP is a meta-register which includes records from the Australian New Zealand Clinical Trials Registry (ANZCTR), the Brazilian Clinical Trials Registry (ReBec), Chinese Clinical Trial Registry (ChiCTR), ClinicalTrials.gov, Clinical Research Information Service (CRiS) - Republic of Korea, Clinical Trials Registry - India (CTRI), Cuban Public Registry of Clinical Trials (RPCEC), EU Clinical Trials Register (EU-CTR), German Clinical Trials Register (DRKS), Lebanese Clinical Trials Registry (LBCTR), Iranian Registry of Clinical Trials (IRCT), ISRCTN, Japan Primary Registries Network (JPRN), The Netherlands National Trial Register (NTR), Pan African Clinical Trial Registry (PACTR), Peruvian Clinical Trial Registry (REPEC), Sri Lanka Clinical Trials Registry (SLCTR), and Thai Clinical Trials Registry (TCTR). Data sets from the ANZCTR, ChiCTR, ClinicalTrials.gov, EU-CTR, ISRCTN, and NTR are updated every week; data from the remaining registries are updated every 4 weeks. We will search the ICTRP after a weekly update, and if needed search records of registries that are less frequently updated individually for the time between last update and search date. To identify additional studies, we will consult content experts.

2.3. Data management and selection process
Two authors will independently screen titles and full records using Microsoft Excel. Disagreements will be resolved by discussion to reach consensus or by involving a third reviewer if needed. Search results, study selection and reasons for excluding records will be presented in a PRISMA flow diagram.[24]

2.4. Data extraction
Standardized forms will be used to extract data by 2 reviewers independently as follows:
- Source of the data: corresponding author or study group, trial registration platform and registration identifier
- Study characteristics: trial design, timing of randomization, study setting, funding, reporting of endpoint adjudication committee, inclusion and exclusion criteria, planned sample size, length of follow-up, recruitment status, estimated study completion date, plan to share individual participant data
- Intervention information: anticoagulant agent and dose, co-interventions if appropriate
- Outcome: primary and secondary outcomes
2.5. Outcomes and prioritization
Studies do not require to specify a certain outcome to be eligible for the review, but all outcomes will be extracted and reported in the review.

2.6. Risk of bias (quality) assessment
Given the purpose of this review and the nature of eligible records, no risk of bias assessment will be performed.

2.7. Data synthesis
Study characteristics will be analyzed using descriptive statistics.
AUTHOR CONTRIBUTIONS
TT has full responsibility over the manuscript. All authors contributed to concept and design of the study. TT drafted the initial manuscript. All authors reviewed and revised the manuscript.

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DISCLOSURES
The authors state that they have no conflict of interest.
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