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Systematic Review

Clinical trials of anticoagulation in COVID-19: a systematic review

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ABSTRACT

A high prevalence of thrombotic events is observed in coronavirus-2019 (COVID-19). Optimal anticoagulation becomes a critical part of treatment and higher-dose prophylactic anticoagulation is being practiced. Prospective evidence to confirm the safety and efficacy of these regimens is lacking. We performed a systematic review of existing studies of anticoagulation in COVID-19. The ClinicalTrials.gov registry, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and the EU Clinical Trials Register (EudraCT) were searched from inception to September 1, 2020. PRISMA guidelines were followed. Qualitative and quantitative analysis were performed. We identified 36 clinical studies involving anticoagulation in COVID-19. Most common study location was the United States (n=12, 33%). Thirty studies were randomized-controlled (83%) of which 22 were open-label. Median sample size was 309 (IQR 139-952) and study duration was 233 days (IQR 174-357). Most common study setting was critical and non-critical care (n=21, 58%). Most common single primary outcome was all-cause mortality (n=15, 42%) but thrombotic events represent the overall most common primary outcome (n=28, 77%). Low molecular weight heparin (LMWH) was the most common agent studied (n=25, 69%) followed by unfractionated heparin (UFH) (n=14, 38.8%) and factor Xa antagonists (n=8, 22.2%). Therapeutic-intensity prophylaxis was the most common dosage regimen studied in comparison to routine thromboprophylaxis dose in 76% and 86% of studies with LMWH and UFH respectively. Five studies (14%) used intermediate-dose prophylaxis. Bleeding is studied as an outcome variable in 19 studies (53%). Our review identifies studies of anticoagulation in COVID-19 and the pharmacological agents used, dosage intensities, and the outcomes analyzed.

Keywords: COVID-19, SARS-CoV2, Arterial thromboembolism, Stroke, Hemorrhage, Antithrombotic therapy

INTRODUCTION

The Coronavirus 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) has resulted in the death of approximately 890,000 people world-wide as of August 20, 2020.[1] The multisystem effects and lethality of COVID-19 are attributed to its ability to cause "cytokine storm", characterised by deregulation and surge of pro-inflammatory cytokines, leading to acute respiratory distress syndrome (ARDS) and multi-organ failure.[2] The systemic inflammation involves endothelial injury and activation of the coagulation system which leads to a hypercoagulable state.[3] An increased prevalence of venous thromboembolism (VTE) is documented in patients with COVID-19, with the highest rates in the critically ill population.[4-6] As a result, optimal anticoagulation becomes a critical part of the treatment protocols used to reduce the risk of thrombotic events.

However, in the absence of evidence-based treatment guidelines for COVID-19, variations in anticoagulation practices have emerged. For instance, some favor the use of intermediate "higher-dose" VTE prophylaxis in-hospital based on key clinical and lab parameters; others recommend the use of VTE risk assessment tools such as Padua and IMPROVE to guide intensity of anticoagulation, while some adhere to existing routine anticoagulation guidelines given the lack of evidence to support higher-dose regimens.[7-11] Consensus statements and interim guidelines for anticoagulation in COVID-19 have been published but with a lack of uniformity. The International Society of Thrombosis and Hemostasis (ISTH) interim guidelines acknowledged the rationale behind higher-dose VTE prophylaxis but did not recommend the same given the lack of prospective data.[12] Other differences in recommendations exist with regards to the use of vascular imaging, the anticoagulant of choice, and the decision to continue anticoagulation after discharge.[11,13-15] Furthermore, the rates of bleeding due to higher-dose VTE prophylaxis regimens in COVID-19 is yet to be studied.

Given the continuing spread of the pandemic and the looming threat of a "second wave" in areas that have now stabilized, prospective studies on anticoagulation become crucial.[16] It is therefore essential to document the ongoing research of anticoagulation in COVID-19 in order to closely follow the emerging evidence and swiftly implement the best available strategy. We performed a systematic review with an aim to identify, characterize, and consolidate the various ongoing clinical studies of anticoagulation in COVID-19.

METHODS

We performed a systematic review with the primary objective to document the various registered clinical studies of anticoagulation in COVID-19 and characterize various study parameters such as study design, study setting, anticoagulation agents used, and study outcomes, among other variables that are discussed below. Using the keywords "COVID-19", "COVID", SARS-CoV2", "anticoagulation", "thrombosis", and "thromboembolism", the ClinicalTrials.gov registry, the WHO International Clinical Trials Registry Platform (ICTRP), and the EU Clinical Trials Register (EudraCT) were searched from inception to September, 2020.

Inclusion criteria

The following inclusion criteria were used: any participant age; any completed, proposed, or ongoing clinical studies; any study design; any study setting including outpatient, inpatient, and critical care settings; participants with clinically suspected or confirmed diagnosed COVID-19, use of any pharmacological anticoagulant agent, and anticoagulation of any dose-intensity. Prematurely terminated studies were included pending publication of results.

Exclusion criteria

The exclusion criteria used were unregistered clinical trials. Studies including pediatric age group participants were excluded.

The databases were screened (by OT) using the aforementioned criteria and the studies appropriate for potential inclusion were retrieved. After elimination of duplicates, studies were examined by two authors (OT and SRL) for inclusion. Conflict resolution was performed by the third author (SRL) for final inclusion in the review (Figure 1).

For the studies included, the following parameters were recorded: study title, primary ID number, other ID number, investigator and/or study group, geographical location, objectives, study design, study setting, study status, proposed start and completion dates, estimated study duration, inclusion and exclusion criteria, sample size, description of experimental arm and comparator or control arm, primary and secondary outcomes, and the pharmacological anticoagulants used, including dosage and route.

The included studies and their corresponding aforementioned variables were recorded in a database. The available data were then stratified into the following variables in the results section: geographical location, study design, study status/phase, study duration, sample size, and the pharmacological agents used and their dosing intensity (standard, intermediate, or therapeutic), studies which include venous or other thrombotic events, stroke, and bleeding as outcome variables. Studies recording thrombotic events as outcome variable were considered to include ischemic stroke and studies including bleeding as an outcome variable will be considered to include intracranial hemorrhage (ICH) as an outcome variable.

Statistical analysis was performed using IBM® statistical package for social sciences (SPSS)® version 22.0 or Microsoft® Excel® 2013 and results were reported as number of events, percentages, ratios, mean, median, and mode.

RESULTS

Studies included

We identified a total of 36 clinical studies that were eligible for inclusion (Figure 1): 31 studies were identified from the ClinicalTrials.gov registry, 3 were retrieved from ICTRP, and 2 were retrieved from the EudraCT database.

Geographical location

Geographic locations of the studies are summarized in Figure 2. The two most common countries with registered studies were the United States of America (12) and Brazil (5).

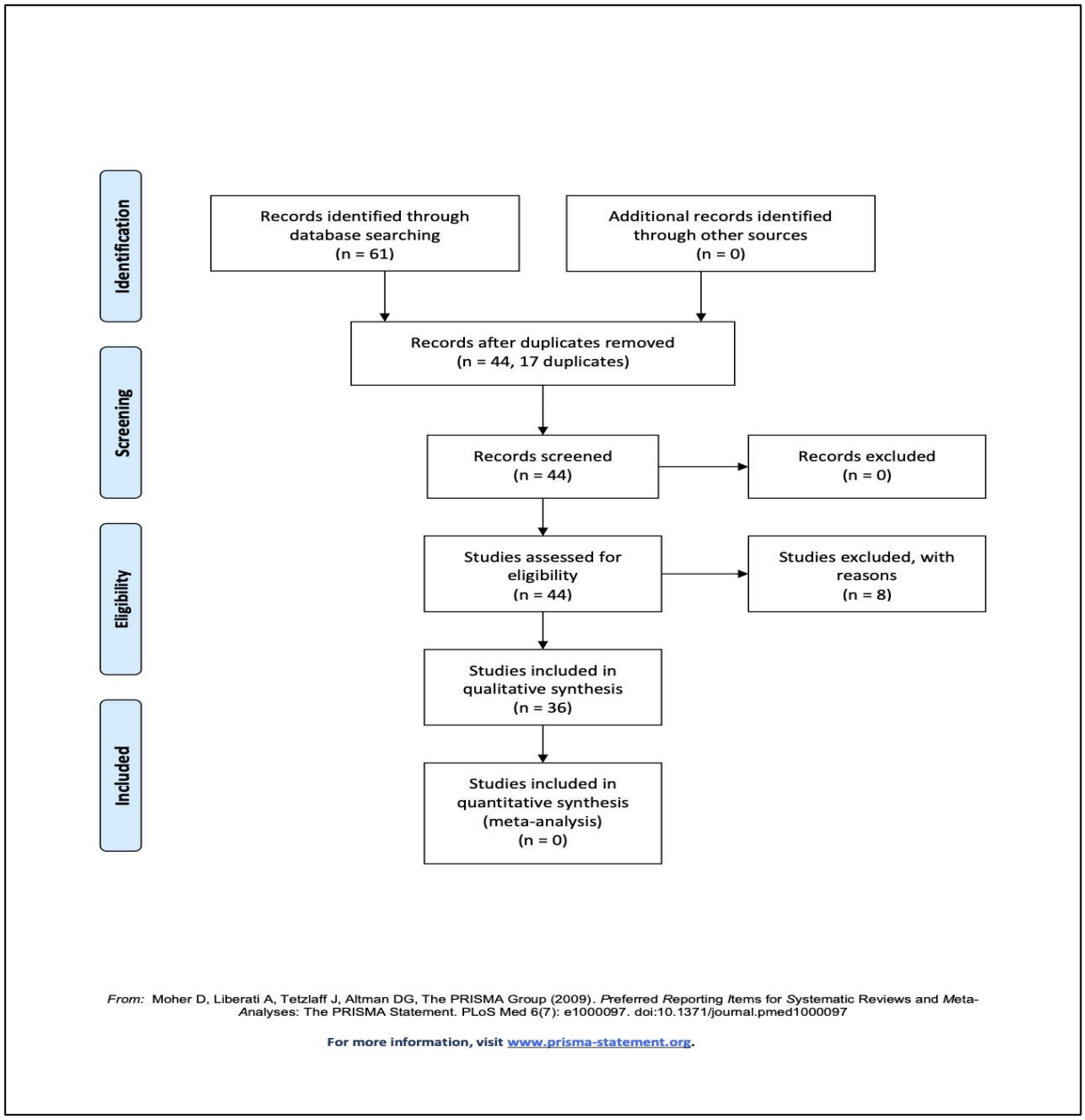

Figure 1: PRISMA flowchart listing the various stages of study screening and inclusion in this systematic review.

Study design

Studies were broadly classified into observational or interventional studies. Of the 32 interventional studies retrieved, we identified 30 randomized controlled, 1 non-randomized controlled, and 1 non-randomized. Of the randomized controlled studies, 3 were single-masking, 1 double-masking, 3 triple-masking, 1 quadruple-masking and 22 open label studies (Figure 3). Of the observational studies, two studies had a retrospective design and one had a prospective design. Design information could not be obtained for one observational study. All four observational studies use non-probability sampling (Figure 3).

Study duration

Estimated duration of the included studies varies between 83 days and ongoing with a median duration of 233 days (IQR 174-357). 11 studies are estimated to be conducted in fewer than six months, 16 studies are of estimated duration between six months and one year, and 5 studies had a stated duration greater than one year. Study duration could not be retrieved for 4 (11%) studies.

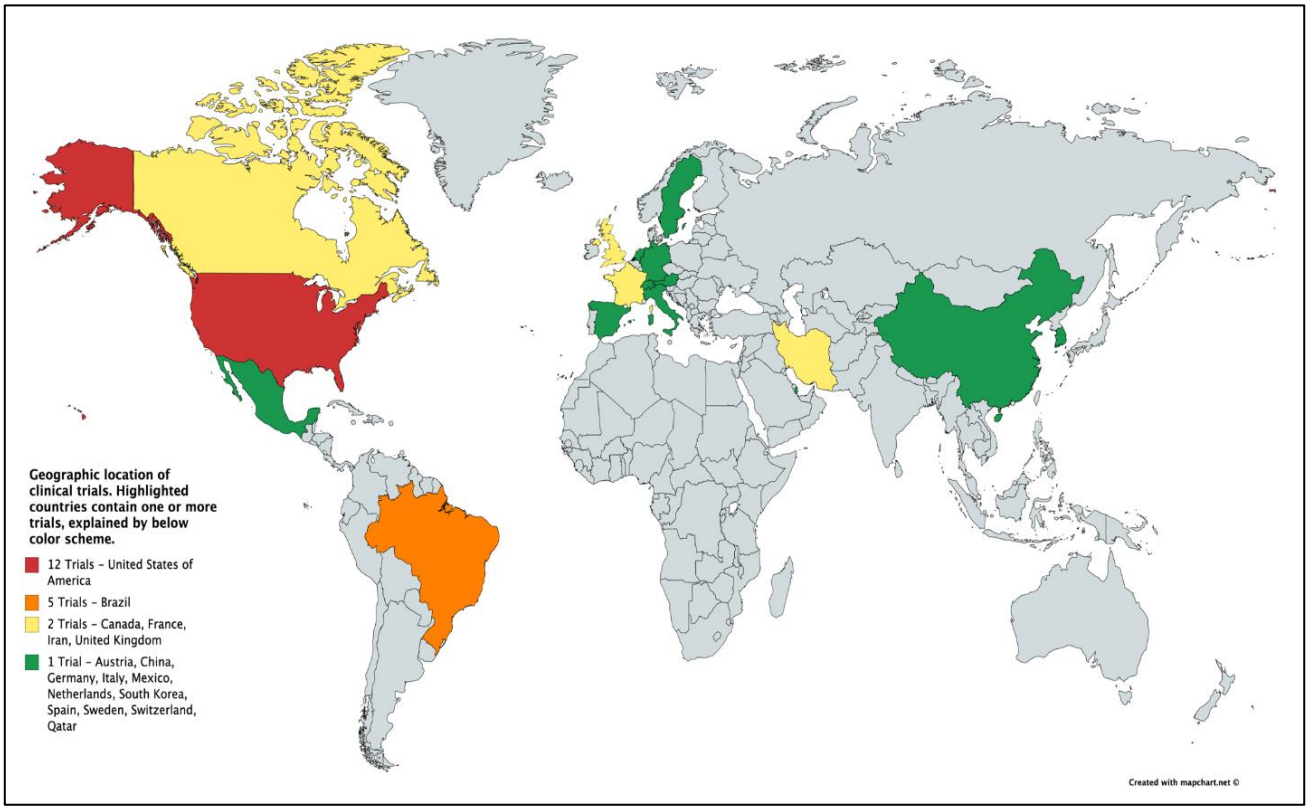

Figure 2: Geographical representation of studies of anticoagulation in COVID-19.

Study setting

Of the 36 studies identified, 9 studies examine critically ill patients with COVID-19, 21 studies examine both critically-ill and non-critically ill hospitalized patients with COVID-19, and 1 study examines non-critically ill hospitalized patients with COVID-19. One study examines effects of anticoagulation in COVID-19 in both hospitalized (critically ill and non-critically ill) and outpatient post-discharge settings. One study only examines COVID-19 patients after hospital discharge. Study setting was not available for 3 (8%) studies (Figure 4).

Study status

Studies are registered in the databases using the following qualifying terms for study status- recruiting (n=22), not yet recruiting (n=9), active-not recruiting (n=2), and completed (n=3). Among the 27 active or completed interventional studies, none are in phase 1, 6 are in phase 2, 12 are in phase 3, and 10 are in phase 4 (Figure 5). Two trials are listed as phase 2 or 3. Study phase information was not available for 2 interventional studies.

Sample size

Of the 36 studies, 35 provide information on estimated enrolment - i.e. sample size. Of the 35 studies, 5 studies estimate enrollment of fewer than 100 participants, 22 studies estimate enrollment of 100 to 1,000 participants, and 8 studies estimate enrollment of over 1,000 participants. The median estimated enrolment of participants in all included studies is 309 participants (IQR 139 - 952). Of the 32 interventional trials, the minimum sample size is 15 and the maximum sample size is 7,100 participants. The median sample size of the interventional trials is 309 (IQR 123 - 808) participants. Sample size of the observational trials ranged from 166 to 300 participants.

Primary and secondary outcomes

The most common primary outcomes among the studies are all-cause mortality (n=15), thrombosis/thrombotic events (n=12), incidence of stroke (n=10), use of mechanical ventilation (n=9), and myocardial infarction (n=6). (Figure 6)

Other primary outcomes identified include: non-invasive positive pressure ventilation, P/F ratio for oxygenation, risk of disseminated intravascular coagulation, pulmonary embolism, cardiac arrest, shock, invasive ventilation, survival without ventilation, ventilator support time, number of days alive, number of days in hospital, number of days with oxygen therapy, clinical improvement, clinical worsening, hospital discharge, decreased D-dimer level, increased oxygenation, increased ventilator compliance, evaluation of gas exchange, biochemical indicators in blood, intubation requiring mechanical ventilation, number participants free of respiratory failure,

organ support free days, transfer to ICU, and predictive of coagulation abnormalities for respiratory failure. Four trials mention major bleeding events as a primary outcome.

The most common secondary outcomes of the studies include major and non-major bleeding (n=16), incidence of stroke (n=15), incidence of thromboembolism (n=14), incidence of myocardial infarction (n=11), and ICU admission or length of stay (n=9) (Figure 7).

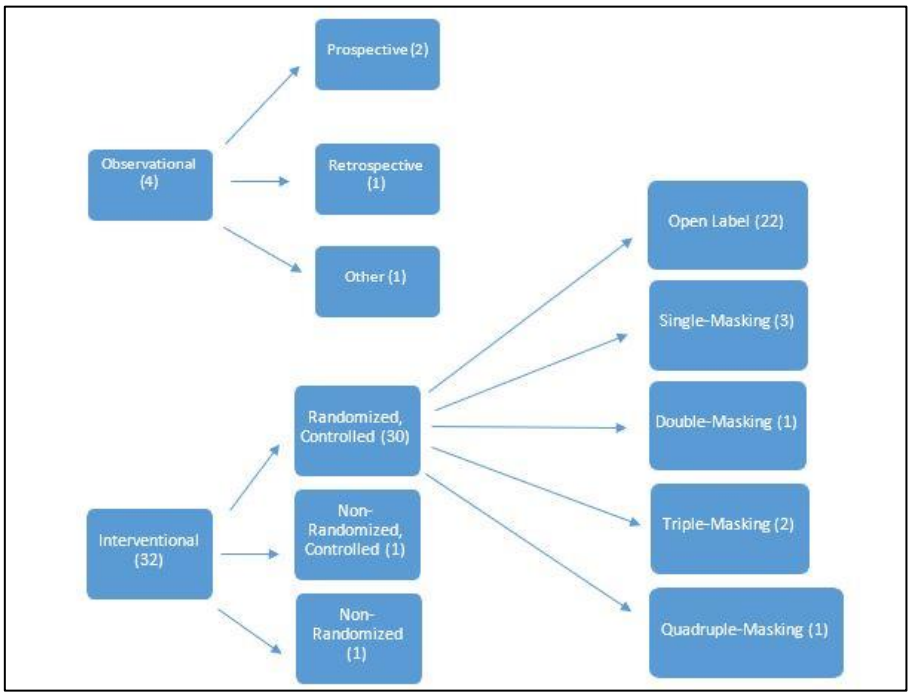

Figure 3: Various designs of anticoagulation studies in COVID-19 (frequencies indicated in parenthesis).

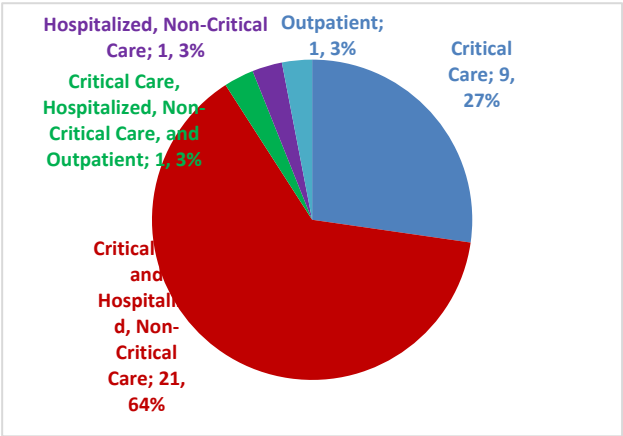

Figure 4: Study settings of anticoagulation studies in COVID-19.

Pharmacological agents

Twenty-seven studies include low molecular weight heparins (LMWH), 21 studies include unfractionated heparin (UFH), 2 studies include direct thrombin inhibitors (DTI), and 10 studies include factor Xa inhibitors. There is one study which evaluates Vitamin K antagonists (Figure 8). Twenty-five studies included either a combination or comparison of the above agents. The various agents in these anticoagulant classes and the doses used are provided below. We identified one study which outcomes with pharmacological thromboprophylaxis will be compared to non-pharmacological mechanical thromboprophylaxis.

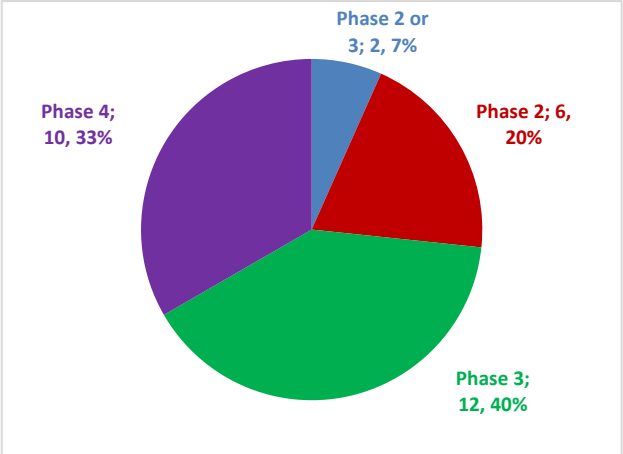

Figure 5: Study phases of anticoagulation studies in COVID-19.

Low-molecular weight heparin (LMWH)

Among the 27 studies involving LMWH as the experimental intervention, Enoxaparin is the most common agent used (22 studies). Other LMWH studied include Tinzaparin (n=4) and Dalteparin (n=4). Three

studies include LMWH that are not specifically identified. There are 19 studies that will analyze therapeutic intensity dosing versus standard of care or prophylactic dosing, 2 studies involve a three-way comparison between prophylactic, intermediate, and therapeutic intensity dosing; 3 studies involve comparison of intermediate versus prophylactic intensity dosing, and 1 study compares therapeutic versus intermediate intensity dosing. Duration of anticoagulation is available from the protocol for 20 studies and ranges between 14 days and 12 weeks. Three studies mention dose titration based on activated partial thromboplastin time levels (aPTT), 7 based on renal function (eGFR and creatinine clearance), 2 based on BMI, and 2 based on factor Xa levels.

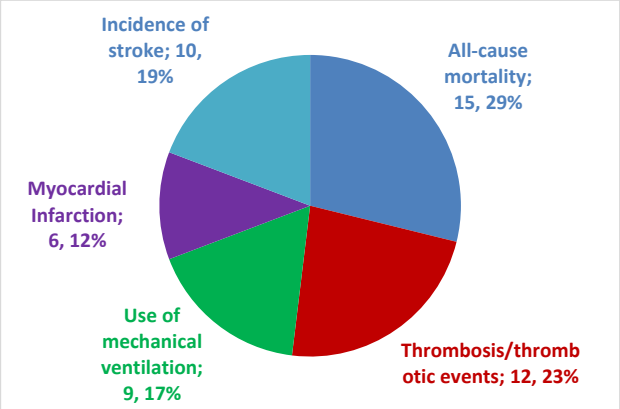

Figure 6: Most common primary outcomes of anticoagulation studies in COVID-19.

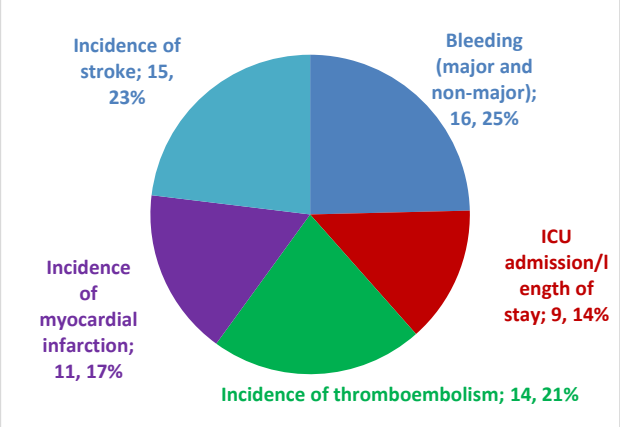

Figure 7: Most common secondary outcomes of anticoagulation studies in COVID-19.

Unfractionated heparin (UFH)

UFH is used as the experimental intervention for anticoagulation in 21 studies. Of these, 17 studies use therapeutic-dose UFH anticoagulation and 3 studies use intermediate-dose UFH anticoagulation to analyze various outcomes, in comparison to standard of care (or) prophylactic-dose anticoagulation. One study compares outcomes with intermediate versus therapeutic dosing. Complete dosing methods for each study are not available for elaboration, however, 3 studies mention dose titration based on aPTT levels and 4 studies titrate dosing based on factor Xa levels. 3 studies adjust dose based on renal function (eGFR and creatinine clearance) and 4 studies based on BMI. Proposed duration of anticoagulation is available for 11 studies, and ranges between 5 days and 30 days. Dosing information was not available for one study.

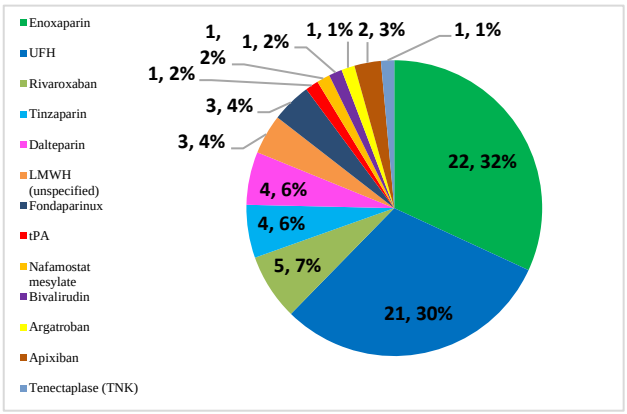

Figure 8: Pharmacological agent used in anticoagulation studies in COVID-19.

Direct thrombin inhibitors (DTIs)

Among the 2 studies including DTIs as experimental intervention, bivalirudin and argatroban are each being used in 1 study. Dosage intensity was not available for bivalirudin. Argatroban will be studied in therapeutic intensity dosage versus standard of care. Institutional protocols will be followed for dosing the DTIs. Duration of anticoagulation ranges between 3 and 30 days.

Factor Xa antagonists

Among the 10 studies involving activated factor X antagonists, Rivaroxaban is the most common agent used in 5 studies. Other factor Xa antagonists studied include Fondaparinux in 3 studies and Apixaban in 2 studies. Rivaroxaban is studied in the following different dosages: oral at 20 mg once daily (adjusted for creatinine clearance or eGFR) and 10 mg once daily. Apixaban is studied in two doses 2.5 mg and 5 mg twice daily. Two studies mentioned dose titration of factor Xa inhibitors based on serum levels.

Vitamin K antagonists

One observational trial studied vitamin K antagonists for anticoagulation in COVID-19 patients when previously initiated for other indications. No dosage information was available.

Thrombolytics

Tissue plasminogen activator (t-PA) is analyzed in one study which compares its outcomes with UFH and standard of care, and is proposed to be dosed at 25 mg

twice intravenously. Another trial studies Tenectaplase (TNK) dosed at 0.25-0.5 mg/kg in comparison to placebo with heparin, both arms titrated to an aPTT of 2.0-2.5 times the upper limit of normal.

Other agents

A new serine protease inhibitor which is currently used for pancreatitis, Nafamostat mesylate, will be used for its anticoagulant properties in one study of COVID-19 patients.

Stroke as outcome

Twenty-five studies list either ischemic stroke or 'thrombotic events', which would include ischemic stroke, as a primary outcome (n=10) or as a secondary outcome (n=15). Sixteen intend to study major bleeding, which would include intracranial hemorrhage (ICH), as an outcome variable. The anticoagulants used in these studies are Enoxaparin (17), UFH (13), Tinzaparin or Dalteparin (5), Rivaroxaban (3), Apixaban (2), and Vitamin K agonists (1).

Bleeding

There were 19 studies that list bleeding as a primary or secondary outcome variable; 15 studies will study only major bleeding, 1 will note only minor bleeding, and 3 will study both. Major bleeding is defined by the ISTH Scientific and Standardization Committee (n=6), by BARC criteria (n=2), by WHO scale (n=1) or remains undefined (n=6), and minor bleeding is not defined. The anticoagulants used in the studies with major bleeding as an outcome variable include Tinzaparin or Dalteparin (n=2), Enoxaparin (n=9), Rivaroxaban (n=1), Fondaparinux (n=2), Argatroban (n=1), Apixaban (n=1), Vitamin K antagonist (n=1) and unspecified LMWH anticoagulation (n=3).

DISCUSSION

Our systematic review documented and summarized, to our knowledge, all global registered studies of anticoagulation in COVID-19. COVID-19 is a new pandemic which has required the use of diverse therapeutic agents and anticoagulation regimens as discussed in previous sections. As a result, it becomes essential to capture all existing studies that analyze the efficacy and adverse effects related to these treatment regimens. We used a broad search strategy to include all geographic regions, study designs, age groups, pharmacological agents, and study outcomes. We identified 36 studies related to anticoagulation in COVID-19 registered in 3 databases - clinicaltrials.gov, WHO ICTRP, and EudraCT. It is assuring to note that there are 36 studies registered over a short time period of 9 months since the onset of the pandemic. Of the 36 studies, 12 studies (33%) were registered from the United States of America, which contributes to approximately a quarter of all diagnosed cases worldwide.[17] Twenty studies (56%) were registered in North and South America, which contribute to approximately half of all diagnosed cases worldwide. We were able to identify only one study from the South East Asian subcontinent despite high prevalence in countries such as India and the origin and high disease prevalence in China.[17] It might be beneficial to conduct retrospective analyses related to various anticoagulation regimens in countries such as China, in order to guide future clinical trials and treatment regimens.

We characterized the various study designs of the registered trials. Thirty studies (83%) use a randomized controlled design which would be optimal to establish the reliability of results. Given the therapeutic nature of the randomized trials and ethical considerations in the setting of the pandemic, blinding is rarely used (20%) and most studies are open-label in design (80%). A median study duration of 232 days indicates possible availability of results within a short period of 7-8 months which could be used to establish anticoagulation guidelines in COVID-19. A median sample size of 309 with a wide range can ensure applicability of results to large hospitalized populations. A majority of studies (n=21) include both critically-ill and non-critically ill hospitalized patients (58%), allowing for the application of emerging results to a wide disease spectrum. Two studies analyze outcomes related to anticoagulation in outpatient settings. Whether COVID-19 leads to a prolonged hypercoagulable state and increased thromboembolic events post-discharge remains to be established.

The single most common primary outcome variable among the studies was all-cause mortality (42%). Thrombotic events (23%) such as stroke (19%) and myocardial infarction (12%) represented the next most common primary outcomes; however, when combined (77%), thrombotic events surpass all-cause mortality as the most common outcome variable studied. The goal of using these agents in higher doses is to combat the high prevalence of thromboembolism in COVID-19.[4-6] Respiratory and ventilator parameters such as P/F ratio, oxygen requirements, and ventilator-free days consisted of the other most common primary outcomes.

Of pharmacological agents used, LMWH represented the most common anticoagulant studied (75%), followed by UFH (58%), and Rivaroxaban (14%). LMWH is known to carry significant advantages over UFH such as ease of administration and predictability of effect.[18] Only one study includes outcomes related to VKA in a retrospective design when used for other indications. VKAs are rarely preferred in COVID-19 possibly due to logistic hardships attached to its use such as laboratory-based INR monitoring which may be difficult during a pandemic. The safety of the newer oral anticoagulants in COVID-19 has been a topic of concern, given its potential interactions with other therapeutic agents such as antivirals and azithromycin, and the lack of established testing to monitor or titrate its anticoagulant effect.[19] Of the various studies and anticoagulants, the most common dosage

regimens compared was therapeutic-level dosing versus standard-of-care thromboprophylaxis dosing, as noted in 19 studies of LMWH (76%) and 17 studies of UFH (81%). Other trials including LMWH and UFH use intermediate-level dosing (n=5), the definition of which is not uniformly established. One study proposes to compare low-dose t-PA versus therapeutic dose anticoagulation and another compares two different doses of tenectaplase with therapeutic dose heparin. Nafamostat mesylate, a novel serine-protease inhibitor with anticoagulant properties, is explored as a therapeutic option in one study.

Despite the use of therapeutic-intensity dosing in approximately 80% of the studies registered, bleeding is proposed as an outcome variable in only 19 studies (53%). DIC is commonly seen in patients with critically-ill COVID-19 and is found to manifest more frequently as a prothrombotic state and organ dysfunction and less commonly with bleeding.[20] Therefore, a growing number of centers have resorted to the use of higher-intensity anticoagulation regimens since the onset of the pandemic. As discussed previously, the rate of bleeding from these regimens and their safety remain unknown. One study of Dalteparin versus UFH documented a bleeding rate of 5.6% in critically-ill COVID patients, however the study used routine thromboprophylaxis dosing.[21] Aside from this, literature on bleeding in COVID-19 is so far restricted mainly to case reports and series.[22-23] It is therefore vital for all the studies of anticoagulation in COVID-19 to consider the inclusion of bleeding as a mandatory outcome variable.

Bauchner and Fontarosa describe several limitations to existing COVID-19 trials, including varied disease manifestations in the critically ill, profound heterogeneity of study protocols, studies of combination regimens of different medications as opposed to individual agents, requirement of a sizeable number needed to treat, and a large share of studies focused at treatment and not prevention.[24] The anticoagulation studies identified in our systematic review may help address the shortcomings raised here. A significantly large median sample size, primary focus on anticoagulant agents without antibiotic combinations, and studies of three major dosage intensity classes are notable strengths of the anticoagulant studies registered. By prospectively analyzing rates of outcomes such as ICU admissions, thromboembolic events, and bleeding, these studies may offer insights into prevention of these hazardous events. However, significant differences are expected between the institutional protocols in their definitions of dosage intensity classes for each drug, which we were unable to retrieve from available protocols and compare in this review, leading to a potential source of persisting heterogeneity. Given the need for prospective data to guide treatment in the midst of a pandemic, it is reasonable to expect significant variations and suboptimal protocols from these swiftly designed trials.

Our systematic review has strengths and limitations. There are currently no comprehensive reviews of anticoagulation studies in COVID-19. Our systematic review offers a compilation of the registered trials, with an objective to serve as a resource to follow up the disease outcomes related to the various anticoagulants and their different dosage intensities. Our study used a validated screening process (PRISMA), with study selection performed by two independent reviewers. We used broad inclusion criteria with an aim to capture all existing studies, especially given the relative lack of anticoagulation treatment literature on this topic.

Study limitations include inability to review all the different dosages, routes, monitoring, and titration methods for the anticoagulants listed, due to the lack of consistent declaration of these parameters in study protocols, and to restrict the manuscript to the stated aim.

CONCLUSION

Our systematic review documents the various studies of anticoagulation in COVID-19 and discusses relevant study parameters such as pharmacological agents, their dosage intensities, and the outcomes analyzed. We aim to provide a compilation of these studies in order to help monitor the results, which may have crucial implications in disease treatment or in the design of future anticoagulation trials in COVID-19.

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Ethical approval: Not required

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