Protocol and Amendments - Systematic Review on Anticoagulation Comparative Studies

Final (v4.0.0): Nov 30, 2021
ASH Review Team

Table of Content

The final review protocol is provided on the following pages. The following changes, and the rational for the changes, were made to the protocol.

Revisions to previous Version 2.0, Sep 3, 2021 (Amendment 02) Date: V4.0.0, Nov 30, 2021 (Amendment 03)				
Section number and title in v2	**Section number and title in Amendment (v3)**	**Original text**	**Changed to**	**Rationale**
4.1 Eligibility (Table 1)	4.1 Eligibility (Table 1)	• Limb amputation • ST-elevation myocardial infarction	• Limb amputation (Acute limb ischemia as a surrogate) • ST-elevation myocardial infarction (acute coronary syndrome as a surrogate)	These additional outcomes are added as a surrogate outcome when direct data are not available
4.1 Eligibility (Table 1)	4.1 Eligibility (Table 1)	NA	• Prasugrel • Ticagrelor	Additional drugs are added to capture all relevant medications for antiplatelet therapy
4.8 Subgroup analysis	4.8 Subgroup analysis	NA	ICEMAN assessment will be performed to evaluate credibility of potential subgroup effects	ICEMAN assessment is used to formally evaluate the credibility of subgroup effects
4.4 Data extraction	4.4 Data extraction	NA	We will request additional unpublished data from trial authors as needed.	This is added to ensure we have all necessary data for all prioritized outcomes to perform an analysis.
4.4 Data extraction	4.4 Data extraction	The form will capture general study details (e.g., type of study, citation, setting), study risk of bias, patient population details (e.g., age, comorbidity	The form will capture general study details (e.g., type of study, citation, setting, use of treatments proven to be effective for COVID-19), study risk of	Additional patient characteristics are added to allow exploratory analysis when possible.

		profile, severity of COVID-19 disease, method of COVID-19 detection, type of anticoagulation and dose intensity)	bias, patient population details (e.g., age, comorbidity profile, severity of COVID-19 disease, method of COVID-19 detection, COVID-19 treatments, type of anticoagulation and dose intensity)	
4.6 Synthesis	4.6 Synthesis	NA	We will prioritize extraction and analysis of RCTs and observational studies providing adjusted estimates. Observational studies providing unadjusted estimates will only be extracted and analyzed if feasible.	Prioritization criteria are added for transparency and feasibility purposes
4.6 Synthesis	4.6 Synthesis	NA	Using RevMan 5.4.1, frequentist random-effects meta-analyses will be conducted for all outcomes according to Cochrane Handbook guidance to allow heterogeneity among studies in effect estimates. A random-effects model with Mantel-Haenszel methods will be used for dichotomous outcomes and inverse variance methods for mean	Details on statistical plans are added for transparency

			difference of continuous outcomes.	
4.7 Sensitivity analysis	4.7 Sensitivity analysis	Study design: RCT vs. prospective cohort vs. retrospective cohort vs. case-control	Study design: RCT vs. prospective cohort vs. retrospective cohort vs. case-control; Adaptive/Bayesian trial design vs conventional trial design (Amendment 03)	Sensitivity analyses will be performed to assess the robustness of the main models

Revisions to previous Version 2.0, Mar 12, 2021 (Amendment 01) Date: V3.0.0, Sep 3, 2021 (Amendment 02)				
Section number and title in v2	**Section number and title in Amendment (v3)**	**Original text**	**Changed to**	**Rationale**
4.1 Eligibility (Table 1)	4.1 Eligibility (Table 1)	Peer reviewed published studies will be included. Abstracts without full text reports	Peer reviewed published studies, preprint and RCT abstracts/conference presentation will be included in the review. Peer reviewed published studies will be included in the main analysis. NRS abstract will be excluded	As of September 1, 2021, research team will include RCT abstracts and preprints. Evidence is still limited. Peer reviewed RCTs are often published in several months post press release (or first online conference abstract). RCT abstracts will be used to get a sense of what future data may look like in terms of the direction of evidence, and

				ultimately recommendations, and to avoid the yo-yo effect. We will analyze data from RCT abstracts in a sensitivity analysis

Revisions to previous Version 1.0, Oct 31, 2020 (Original protocol) Date: V2.0.0, Mar 12, 2021 (Amendment 01)				
Section number and title in v1	**Section number and title in Amendment (v2)**	**Original text**	**Changed to**	**Rationale**
Not in the protocol.	NA	NA	NA	Systematic review protocol cannot be registered anymore because data abstraction has been started at the time of submission.
2 Background	2 Background	Similarly, it would be helpful to explore whether the anticoagulation effects in COVID-19 patients are different from those in critically ill or acutely ill patients This protocol describes an initial and living systematic review addressing the desirable and undesirable health effects of anticoagulation therapy in adult patients	Similarly, it would be helpful to explore whether the anticoagulation effects in COVID-19 patients are different from those in critically ill, acutely ill, and discharged patients. This protocol describes an initial and living systematic review addressing the desirable and undesirable health effects of antithrombotic therapy in adult patients	As of February 2, 2021, research team will also address PICO 3 as ASH has approved the additional of PICO 3 (discharged patients)

		with COVID-19 who are critically ill or acutely ill.	with COVID-19 who are critically ill, acutely ill, or being discharged from hospital.	
3 Research Questions	3 Research Questions	NA	3. What are the desirable and undesirable effects of post-discharge prophylactic-intensity vs. no antithrombotic therapy in adults with COVID-19 who are being discharged from hospitalization for COVID-19 related critical or acute illness?	Same as above
4.1 Eligibility (Table 1)	4.1 Eligibility (Table 1)	NA	**Population:** • Being discharged from hospitalization for COVID-19 related critical or acute illness **Exposure (anticoagulation)** 3. any prophylactic-intensity antithrombotic regimen with no antithrombotic/placebo, for patients being discharged from hospitalization for COVID-19 related critical or acute illness. Exclusion: - For Critically and Acutely ill patients: studies	Same as above

			assessing the effect of antiplatelet therapy. - For patients being discharged: studies assessing different antithrombotic intensities. **Outcomes:** Some outcomes are not relevant for all three PICO questions. • Re-admission to hospital	
4.2 Search Sources and Strategy (Table 2)	4.2 Search Sources and Strategy (Table 2)	NA	As of February 2, 2021, we will continue to prioritize RCTs. Ongoing trials will be tracked. To capture ongoing trials, we will search Cochrane COVID-19, Epistemonikos, Prospero, and WHO Global research database every 2-3 months. (Amendment 01)	In response to the press release on the preliminary results of the ATTACC, ACTIV-4 and REMAP-CAP trials the team agreed to explore the feasibility of obtaining the trial data and possibly conducting an individual patient data meta-analysis (IPDMA). To achieve this, we need to identify ongoing trials that will answer our research questions and invite the trialists to collaborate and share data with us to produce timely recommendations and reduce time-to-publication.

4.2 Search Sources and Strategy (Table 2)	4.2 Search Sources and Strategy (Table 2)	Preprints (available through bioRxiv, MedArXiv, or JIMIR preprints) may be sought and incorporated but will not be searched a priori	Preprints (available through bioRxiv, MedArXiv, or JIMIR preprints) will not be searched a priori, but may be used to identify upcoming peer-reviewed papers	To support IPDMA initiatives
4.5 Risk of bias assessment	4.5 Risk of bias assessment	In the Phase I rapid review, studies will be assessed by one person and uncertainties verified by a senior team member. In the Phase II living review, risk of bias will be assessed by two independent reviewers, and disagreements will be resolved by a senior team member.	In the Phase I rapid and II living review, studies will be assessed by one person and uncertainties verified by a senior team member.	Feasibility reasons
NA	4.9 Potential individual patient data meta-analysis (IPDMA)	NA	If review timelines allow, it will be explored if clinical trial leaders are willing to share trial data for individual patient data meta-analysis.	Same as above

PICO 1-3 specification: https://www.dropbox.com/s/mutrkhnsyfgive8/PICOs%201-3%20specification_3-MAR-2021.docx?dl=0

1 ANTICOAGULATION IN CRITICALLY, ACUTELY ILL, AND DISCHARGED PATIENTS

2 BACKGROUND

The American Society of Hematology (ASH) aims to develop a rapid, living clinical practice guideline for the use of anticoagulation in adult patients with COVID-19. Patients with COVID-19 appear to be at increased risk for experiencing venous thromboembolism (VTE) and other thromboembolic complications compared with other patients with similar severity of illness.[1,2] VTE, which includes pulmonary embolism (PE) and deep venous thrombosis (DVT), has a substantial risk of death and recurrent event, especially in patients who have high risk factors, and requires short-term treatment and long-term prophylaxis of recurrences.[3-5] Micro thromboembolic complications may play a role in the cause of hypoxemic respiratory failure and death.[1] Practitioners are using a variety of primary prophylactic anticoagulation practices in the absence of trustworthy COVID-19 specific guidance.[6-9] Trustworthy recommendations are based on the best available research evidence, and are formulated following a systematic and transparent process using best practices in guideline development, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[10]

Recent ASH clinical practice guidelines addressed 10 different topics regarding VTE management, using both advanced and innovative methods to ensure trustworthiness, transparency, user-friendliness, and rigor.[11] Although developed prior to the COVID-19 pandemic, these guidelines may inform current practice in COVID-19 patients. However, there is a need for COVID-19 specific recommendations considering the potential different pathophysiology, different or additional risk factors for VTE, and higher risk for adverse effects of anticoagulation in COVID-19 patients compared to the general population.[7] In addition, given the observed propensity for VTE in COVID-19 patients, practitioners are raising new questions (i.e., not addressed in the ASH VTE guidelines) relating to choices of anticoagulant type and intensity.[6,8,9]

To ensure the trustworthiness of the ASH COVID-19 guidelines, it will be crucial to have reliable estimates for the effect of anticoagulation strategies on patient-important outcomes, e.g., mortality, VTE, major bleeding, and potentially others. In addition, it is important to know if this effect varies among important subgroups of COVID-19 patients. Similarly, it would be helpful to explore whether the anticoagulation effects in COVID-19 patients are different from those in critically ill, acutely ill, and discharged patients. (Amendment 01)

This protocol describes an initial and living systematic review addressing the desirable and undesirable health effects of antithrombotic therapy in adult patients with COVID-19 who are critically ill, acutely ill, or being discharged from hospital. (Amendment 01)

3 RESEARCH QUESTIONS

1. What are the desirable and undesirable effects of prophylactic-intensity vs. intermediate-intensity vs. therapeutic-intensity anticoagulation in adults with COVID-19 who are critically ill?
2. What are the desirable and undesirable effects of prophylactic-intensity vs. intermediate-intensity vs. therapeutic-intensity anticoagulation in adults with COVID-19 who are acutely ill?

3. What are the desirable and undesirable effects of post-discharge prophylactic-intensity antithrombotic vs. no antithrombotic therapy in adults with COVID-19 who are being discharged from hospitalization for COVID-19 related critical or acute illness? (Amendment 01)

4 METHODS

This protocol was developed based on previous work for the ASH guidelines on the management of VTE, and with input of clinical experts and patient representatives as part of the ASH anticoagulation in COVID-19 guideline panel. The review will address the three research questions and will be performed in two phases. We will indicate it when methods apply to only one research question, and which methods are relevant for each phase:

1. Phase I – Initial review: initially we will develop the 'base' (or 'baseline') review. This process will be achieved by following the usual systematic review process with a large team at high speed, to inform GRADE Evidence Profile and Summary of Findings tables for the guideline questions of interest. The methods for the review are written to allow modifying some aspects of the process according to the nature and volume of the evidence, notably for language of the full text report, study design, literature sources searched, and electronic availability of full text reports.
2. Phase II – Living review: following phase I, a living systematic review process will ensue to update the initial reviews on a continual basis. During the living review process, steps that were performed at high speed will now be completed with more time. Any potential restrictions made in Phase I will be considered for inclusion in Phase II.

4.1 Eligibility

We will include studies meeting the eligibility criteria as outlined in Table 1.

Table 1. Eligibility criteria.

	Inclusion	Exclusion
Population	COVID-19 & absence of VTE • Adults (18 years of age or over) with suspected or confirmed COVID-19 (WHO definition[12]), with or without comorbidities • Patients should not have confirmed or suspected VTE at enrolment COVID-19 disease severity At study baseline, these patients can be: • At study baseline, these patients can be: • Critically ill requiring hospitalization • Acutely ill requiring hospitalization • Being discharged from hospitalization for COVID-19 related critical or acute illness (Amendment 01) Disease severity will not be linked to specific settings (ICU, general ward, community) given patients with specific level of	Other coronavirus conditions, such as SARS and MERS. Certainty that the outcomes occurred before detection of suspected or confirmed COVID-19.

	disease severity may not be treated in the usual setting due to overcrowding conditions. Our definition of critical illness will be based on the need for respiratory or cardiovascular failure that without therapy would probably lead to death. <u>Timing of COVID-19 diagnosis or positive SARS-CoV-2 test</u> Patients may have had VTE as the primary diagnosis on presentation to a clinic. If COVID-19 diagnosis or positive SARS-CoV-2 test were found on the same day, or symptomatic history suggested that COVID-19 was present before the VTE, patients will be included.	
Exposure (anticoagulation)	Studies comparing: 1. at least two of: 1) prophylactic-intensity anticoagulation: 2) intermediate-intensity anticoagulation; 3) therapeutic-intensity anticoagulation, or 2. any anticoagulation regimen with no anticoagulation/placebo. This includes studies whereby the event rates are not separately reported for different AC intensities, but the event rates for any AC and no AC/placebo are separately reported. 'Any AC' can also include a clinic's specific anticoagulation strategy/protocol, or 3. any prophylactic-intensity antithrombotic regimen with no antithrombotic/placebo, for patients being discharged from hospitalization for COVID-19 related critical or acute illness. (Amendment 01) <u>Types of anticoagulant to be included & intensity categorization</u> The following medications will be included for patients receiving anticoagulation/antiplatelet therapy: - Low molecular weight heparin - Unfractionated heparin - Fondaparinux - Apixaban - Dabigatran - Edoxaban - Rivaroxaban - Argatroban - Bivalirudin - Vitamin K antagonist - Aspirin - Clopidogrel - Prasugrel (Amendment 03) - Ticagrelor (Amendment 03)	For Critically and Acutely ill patients: studies assessing the effect of antiplatelet therapy. For patients being discharged: studies assessing different antithrombotic intensities. (Amendment 01)
Outcomes	The outcomes of interest were prioritized as critical for anticoagulation decision-making using a standard GRADE process for selecting and ranking outcomes, based on a previous ASH guideline on VTE management and	Patient outcomes that were not rated as being 'critical' for

	supplemented based on core outcome sets for COVID-19 research and expertise of the current panel members. Some outcomes are not relevant for all three PICO questions. Incidence of one or more of the following critical outcomes • All-cause mortality • Pulmonary thromboembolism • Deep vein thrombosis (any site) • Major bleeding (including gastrointestinal bleeding) • Hemorrhagic stroke/intracranial hemorrhage • Heparin-induced thrombocytopenia • Multiple organ failure • Re-admission to hospital (Amendment 01) • ICU admission • Limb amputation (Acute limb ischemia as a surrogate) (Amendment 03) • Invasive ventilation • Non-invasive ventilation • Dialysis • Ischemic stroke • ST-elevation myocardial infarction (acute coronary syndrome as a surrogate) (Amendment 03) • Non-ST-elevation myocardial infarction • Peripheral arterial disease Reporting of outcomes may vary and include global (e.g., unspecified VTE/extremity), unspecified severity, 'symptomatic' versus 'asymptomatic', or a composite of various outcomes. Where applicable, assumptions may be considered. As to whether, or to what extent, reporting variations (such as global, unspecified, or composite events) are abstracted during data collection will depend on the volume of more adequately reported outcomes. Standardized outcome definitions and marker states will be not be used during data collection, but outcomes will be collected as reported by authors whereby the definition and assessment will be recorded. We will then assess the indirectness compared to established health outcome descriptors. No minimum length of follow-up for inclusion will be applied.	anticoagulation decision-making
Setting	Any setting	
Study design	• Randomized controlled trials, reporting the outcomes of interest in relevant patient groups	Studies not comparing at least two of the

	• Observational comparative studies, reporting outcomes of interest in relevant patient groups. This can include prospective cohort, retrospective cohort, and case-control studies RCTs will be given priority, but given the short timeframe since onset of the pandemic, we do not expect to find many relevant high-quality RCTs and we will also include observational comparative studies. Systematic reviews on the effect of anticoagulation in the populations of interest will be checked for relevant individual studies.	anticoagulation intensity groups.
Publication types	Peer reviewed published studies, preprints and RCT abstracts/conference presentation will be included in the review. Peer reviewed published studies will be included in the main analysis. (Amendment 02)	NRS abstracts
Language	Any language. If language restrictions are applied for feasibility of conducting the Phase I initial review, those reports will be included during the Phase II living update. We anticipate having adequate resource support for language translation for the duration of the living review.	
Publication or Report Date	As of December 2019 onwards, to coincide with the first identification of COVID-19	

4.2 Search Sources and Strategy

We will search the following general bibliographic databases: MEDLINE (Ovid), EMBASE (Ovid), SCOPUS.

In addition, we will search databases dedicated to COVID-19: Cochrane COVID-19 study register, CYTEL map of ongoing clinical trials, Epistemonikos COVID-19 (LOVE platform), and the WHO Global [COVID-19] Research Database.

Table 2. Databases & considerations

	Phase I	**Phase II**
Databases	MEDLINE, EMBASE, Epistemonikos Cochrane COVID-19 study register, WHO Global Covid-19 research database	MEDLINE, EMBASE, Epistemonikos, Cochrane COVID-19 study register, WHO Global Covid-19 research database will be searched on an ongoing basis, with results collated monthly. If the number of monthly results are sufficiently large (e.g. > 5000 citations), the strategy may be revised to be more specific and/or machine

		learning algorithms used to prioritize results. As of February 2, 2021, we will continue to prioritize RCTs. Ongoing trials will be tracked. To capture ongoing trials, we will search Cochrane COVID-19, Epistemonikos, Prospero, and WHO Global research database every 2-3 months. (Amendment 01)
Considerations	OVID Methodology filters will be applied to MEDLINE and EMBASE searches. Results will be limited, where possible, to database records entered ≥ December 2019	Additional databases will be searched periodically, as feasible. Preprints (available through bioRxiv, MedArXiv, or JIMIR preprints) will not be searched a priori, but may be used to identify upcoming peer-reviewed papers.

For the Phase I review, we will scan their references for individual studies. Systematic reviews will be defined according to the definition outlined in the WHO Handbook for Guideline Development (2012). Eligible reviews will have "a specific and clearly focused question (in PICO format); an explicit, reproducible method including pre-defined eligibility criteria; a comprehensive, exhaustive and systematic search for primary studies; a selection of studies using clear and reproducible eligibility criteria; critical appraisal of included studies for quality; and a systematic presentation and synthesis of the characteristics and findings of the included studies." Those reviews will have searched in a minimum of two bibliographic databases.

For practical consideration for the review, only electronically-available reports will be included; any outstanding reports will be ordered via interlibrary loan for the Phase II living update.

The search strategies will be based on a combination of controlled vocabulary (e.g., MeSH) and free text terms (as applicable). Using sample relevant articles we will refine these search strategies. The search strategies will be developed initially in MEDLINE and peer-reviewed using PRESS prior to implementation and translation to other databases.

4.3 Study selection

Multifile downloads from bibliographic databases will be de-duplicated in EndNote prior to uploading to Covidence (https://www.covidence.org/). Each title-and-abstract record will be screened by two independent persons for potential relevance. In case of disagreement, references are included for full-

test screening. All potentially relevant full text reports will be screened by two independent persons. Disagreements will be resolved by a senior team member. A pilot process using the first 100 title/abstract records and 10 full text articles on standardized screening forms will be used to calibrate the research team. Reports that are co-publications or multiple reports of the same study will be identified as such.

4.4 Data extraction

A focused data extraction form will be developed and piloted among the research team using a sample of five studies for calibration. The form will capture general study details (e.g., type of study, citation, setting, COVID-19 treatments (Amendment 03)), study risk of bias, patient population details (e.g., age, comorbidity profile, severity of COVID-19 disease, method of COVID-19 detection, type of anticoagulation and dose intensity), and per outcome: definition/assessment, duration of follow-up, measure of association, and subgroup effects. Extractions will be performed by one reviewer and verified by a second reviewer. Disagreements will be resolved by a senior team member.

We will request additional unpublished data from trial authors as needed. (Amendment 03)

4.5 Risk of bias assessment

Risk of bias for RCTs will be assessed using the Cochrane RoB 2.0 tool. Risk of bias for observational comparative studies will be assessed using ROBINS-I.

In the Phase I rapid and II living review, studies will be assessed by one person and uncertainties verified by a senior team member. The pilot phase of the same five studies for the extraction pilot will calibrate the team also for risk of bias assessment.

Important potential confounders in observational studies: to assess whether prognostic factor analysis was adjusted for important confounders as known for non-COVID-19 patients, the factors identified by Darzi et al.[15] will be used for the outcomes of VTE and Major bleeding:

- **For VTE-related outcomes:** Age, Previous VTE, Thrombophilia, Lower limb paralysis, Reduced mobility/immobilization, Current cancer, intensive/critical care unit (ICU/CCU) stay, Recent (≤1-month trauma and/or surgery), Obesity, Ongoing hormonal treatment, Acute infection and/or rheumatologic disorder, Acute MI and/or ischemic stroke, Heart and/or respiratory failure
- **For bleeding outcomes:** Gastro-duodenal ulcer, Bleeding prior 3 months, Admission platelets levels, Hepatic failure, ICU/CCU stay, central venous catheter, Rheumatic diseases, Current cancer, Sex, Age, glomerular filtration rate (GFR)

4.6 Synthesis

Results will be stratified based on population differences as specified in the guideline PICO questions, i.e. according to baseline COVID-19 disease severity, comorbidity or high risk factor (i.e. pregnancy), and thromboprophylaxis type or intensity. General study characteristics will be reported in tables using

appropriate measures (e.g., frequency and proportion, means and standard deviations, medians and interquartile ranges) with accompanying descriptive text.

We will use GRADE to assess the certainty of evidence for comparisons. The overall certainty of the evidence will be assessed across all included studies for a specific outcome and will include judgments regarding risk of bias, indirectness, inconsistency, imprecision, and factors that may increase certainty (large effect, dose-response gradient, or plausible residual confounding).

Results will be reported using the following hierarchy:

RCTs

Event rates will be combined in meta-analysis to calculate a pooled effect estimate (RR, OR, SMD) for research questions #1-3.

Non-randomized evidence - Adjusted measures of association

Studies reporting adjusted measures of association (RR, OR, SMD) for research questions #1-3 will only be pooled if deemed appropriate, i.e. if they were performed in comparable populations with comparable anticoagulation strategies, and adjusted for comparable confounders.

Non-randomized evidence - Unadjusted measures of association

Unadjusted measures of association will be combined in meta-analysis to calculate a pooled effect estimate (RR, OR, SMD) for each research question.

We will prioritize extraction and analysis of RCTs and observational studies providing adjusted estimates. Observational studies providing unadjusted estimates will only be extracted and analyzed if feasible. (Amendment 03)

Using RevMan 5.4.1, frequentist random-effects meta-analyses will be conducted for all outcomes according to Cochrane Handbook guidance to allow heterogeneity among studies in effect estimates. A random-effects model with Mantel-Haenszel methods will be used for dichotomous outcomes and inverse variance methods for mean difference of continuous outcomes. (Amendment 03)

If feasibility, poor reporting, or data distribution precludes pooling of studies in any of the three categories above, effect estimates will be reported narratively.

4.7 Sensitivity analysis

Sensitivity analyses will be considered based on the following factors. If not possible in the Phase I initial review, we will analyze this in the Phase II living review:

- Diagnosis of COVID-19: laboratory confirmed diagnosis vs. suspected diagnosis[12]
- Risk of bias: studies with low risk of bias vs. moderate/high risk of bias
- Study design: RCT vs. prospective cohort vs. retrospective cohort vs. case-control; Adaptive/Bayesian trial design vs conventional trial design (Amendment 03)
- Study size: studies with fewer than 5 outcome events vs. studies with 5 or more outcome events
- If relevant:

- Direct comparison vs network meta-analysis effect
- Event rates with using different clinic protocols (without having a comparison)

4.8 Subgroup analysis

Heterogeneity will be explored using subgroup analyses, which can include type or dose of thromboprophylaxis, severity of COVID-19, comorbidities, among others.

ICEMAN assessment will be performed to assess credibility of potential subgroup effects. (Amendment 03)

4.9 Potential individual patient data meta-analysis (IPDMA)

If review timelines allow, it will be explored if clinical trial leaders are willing to share trial data for individual patient data meta-analysis.

5 REFERENCES

1. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020;46(6):1089-1098.
2. Poissy J, Goutay J, Caplan M, et al. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. *Circulation.* 2020;142(2):184-186.
3. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet.* 2003;362(9383):523-526.
4. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). *Am J Med.* 2014;127(9):829-839 e825.
5. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. *Am J Med.* 2013;126(9):832 e813-821.
6. Cattaneo M, Bertinato EM, Birocchi S, et al. Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified? *Thromb Haemost.* 2020.
7. Pesavento R, Ceccato D, Pasquetto G, et al. The hazard of (sub)therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: the Padua province experience. *J Thromb Haemost.* 2020.
8. Wijaya I, Andhika R, Huang I. Hypercoagulable state in COVID-19 with diabetes mellitus and obesity: Is therapeutic-dose or higher-dose anticoagulant thromboprophylaxis necessary? *Diabetes Metab Syndr.* 2020;14(5):1241-1242.
9. Viecca M, Radovanovic D, Forleo GB, Santus P. Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. *Pharmacol Res.* 2020;158:104950.
10. Siemieniuk R GG. What is GRADE? *BMJ Best Practice* https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/, 2020.
11. Wiercioch W, Nieuwlaat R, Akl EA, et al. Methodology for the American Society of Hematology VTE guidelines: current best practice, innovations, and experiences. *Blood Adv.* 2020;4(10):2351-2365.
12. Organization WH. Global surveillance for COVID-19 caused by human infection with COVID-19 virus: interim guidance. 2020; https://www.who.int/publications/i/item/global-surveillance-for-covid-19-caused-by-human-infection-with-covid-19-virus-interim-guidance, 2020.
13. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med.* 2013;158(4):280-286.
14. Wolff RF, Moons KGM, Riley RD, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann Intern Med.* 2019;170(1):51-58.
15. Darzi AJ, Karam SG, Charide R, et al. Prognostic factors for VTE and bleeding in hospitalized medical patients: a systematic review and meta-analysis. *Blood.* 2020;135(20):1788-1810.
16. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med.* 2010;29(29):3046-3067.