Supplement 8. Protocol for Baseline Risk Review

COVID-19 - Baseline Risk and Prognostic Factors Systematic Review

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Amendment with changes since PROSPERO registration: see last page

BACKGROUND

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 clinical practice guidelines by the American Society of Hematology 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 evidence to guide practice 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 existing VTE guidelines) relating to choices of anticoagulant type and intensity.[6,8,9]

As a foundation to develop recommendations for COVID-19 patients, we need to first have reliable estimates for the baseline risks of patient-important outcomes, e.g., mortality, VTE, major bleeding, and potentially others. In addition, it is important to know if the risk factors modifying such risks are of the same magnitude as in other patients in comparable settings. Similarly, it would be helpful to explore whether there are important prognostic factors in COVID-19 patients that are different from those in other patients.

We will perform an initial and living systematic review w to obtain baseline risk incidence rates for critical outcomes and important risk factors modifying such risk, in adults with COVID-19, which is described in this protocol.

RESEARCH QUESTIONS

1. What is the incidence of outcomes that are critical for anticoagulation decision-making in adults with COVID-19?
2. What are the important risk factors that modify the risk of outcomes which are critical for anticoagulation decision-making in adults with COVID-19?

METHODS

This protocol was developed based on previous work for guidelines on the management of VTE, and with input of clinical experts. The review will address the two 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.

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: • Any acutely ill requiring hospitalization • Critically ill requiring advanced clinical support • Moderately/mildly ill, including: o Patients being discharged o Patients who were never hospitalized Disease severity will not be linked to specific settings (ICU, general ward, community) given patients with specific level	Other coronavirus conditions, such as SARS and MERS. Certainty that the outcomes occurred before detection of suspected or confirmed COVID-19.

	of 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. <u>Anticoagulation therapy & intensity</u> We will include studies of patients managed with or without anticoagulation, to allow flexibility for guideline questions that will be prioritized. With our guideline questions we will compare anticoagulation with no anticoagulation, as well as different intensities of anticoagulation with each other: prophylactic, intermediate, and therapeutic intensity. The related doses will differ depending on the type of anticoagulant. An event rate estimate in patients receiving prophylactic intensity anticoagulation could serve as an appropriate baseline risk estimate for a guideline question addressing prophylactic- versus therapeutic-intensity, whereas patients receiving no anticoagulation would be appropriate for a guideline question addressing whether or not to administer anticoagulation. <u>Types of anticoagulant</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	
Exposure (prognostic factors)	Studies only reporting incidence of outcomes of interest will be included (research question #1), as well as studies reporting potential prognostic factors for outcomes of	

	interest (research question #2). In Phase I, we will include studies reporting prognostic factors for the occurrence of first-time VTE. If the number of included studies is manageable in Phase I, we will also include prognostic factors for all-cause mortality, and possibly other outcomes. If the number of included studies is large, we will extract prognostic factors for other outcomes than VTE in Phase II. Potential prognostic factors for VTE can include, but are not limited to: - Demographics (e.g. age, sex) - Socio-economic factors (e.g. income, insurance status) - Comorbidities (e.g. hypertension, diabetes, obesity, cardiovascular disease) - Biomarkers (e.g. d-dimer, aPTT) – using cut-off values as reported by authors - Interventions (e.g. for COVID-19) - Pregnancy status - Risk modifying behaviour (e.g. smoking)	
Outcomes	Incidence of one or more of the following critical outcomes will be assessed: • All-cause mortality • Pulmonary thromboembolism • Deep vein thrombosis (any site) • Major bleeding (including gastrointestinal bleeding) • Hemorrhagic stroke • Heparin-induced thrombocytopenia • Multiple organ failure • Hospitalization (and duration) • ICU admission (and duration) • Limb amputation • Invasive ventilation • Non-invasive ventilation • Dialysis • Cerebral vein thrombosis • Mesenteric vein thrombosis • Portal vein thrombosis • Ischemic stroke • Myocardial infarction (STEMI and NSTEMI) • Peripheral arterial disease • Functional status impairment 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.	Patient outcomes that were not rated as being 'critical' for anticoagulation decision-making

	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.	
Setting	Any setting	
Study design	• In general, eligible studies reporting on outcome incidence should - to a reasonable extent - report on an unselected sample of the population of interest. Ideally, this would be inception cohorts, but considering potential limitations in the current evidence base, we will include the designs below • Natural history or clinical course (single-arm) cohort studies, not selected based on specific COVID-19 treatment administration • Comparative cohort studies (comparison with a different group of patients): only use COVID-19 group • Studies defined as 'case series' of more than 10 patients: only if COVID-19 patients were enrolled consecutively, i.e. similar to single-arm cohort study (we will increase this sample size for inclusion if the total number of enrolled patients for a given risk factor or baseline risk exceeds 1000 patients. • Case-control: only for the assessment of prognostic factors (research question #2), not incidence • Systematic reviews reporting on individual studies of the designs above to extract data from individual studies without duplicating the use of individual studies to derive risk estimates. In absence of the above observational studies of sufficient quality, we may use data from: • Randomized controlled trials, reporting the outcomes of interest in relevant patient groups, whereby the control group (placebo, usual care, no intervention) will be used Given the short timeframe since onset of the pandemic, we do not expect to find prospective inception cohorts or risk	Studies measuring prevalence; ecological studies; case reports; single-arm cohort/case series selecting patients who received a specific medication to treat COVID-19 Examples of specific COVID-19 targeting treatments (but not limited to this list): - Antivirals (such as remdesivir) - Immunosuppressive (such as glucocorticoids [dexamethasone]) - Antimalarials (such as hydroxychloroquine)

	score modeling (development, validation, impact). However, if identified, such studies will be included in either phase and any risk assessment modelling studies will be used to derive baseline risk estimates or summaries of risk factor studies.	
Publication types	Peer reviewed published studies will be included. If no studies are found, we will seek evidence from (in separate searches): - Unpublished electronic open access articles (MedRxiv, others) - Government organization reports (international, regional) - Randomized controlled trials	Abstracts without full text reports; Commentaries; Letters; Reply to author
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	

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, SCOPUS Cochrane COVID-19 study register, CYTEL map of ongoing clinical trials, WHO Global Covid-19 research database	MEDLINE, EMBASE, Cochrane COVID-19, will be searched on an ongoing basis, with results collated monthly
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) may be sought and and incorporated but will not be

		searched a priori

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.

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.

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), study risk of bias, patient population details (e.g., age, comorbidity profile, severity of COVID-19 disease, method of COVID-19 detection, receipt of anticoagulation and dose), and per outcome: definition/assessment, duration of follow-up, incidence rate or cumulative incidence. Extractions will be performed by one reviewer and verified by a second reviewer. Disagreements will be resolved by a senior team member.

For research question #2, measures of association of potential prognostic factors with the outcome (adjusted or unadjusted) will be extracted. Potential prognostic factors to be included: see Table 1, list may expand during extraction.

If a substantial number of eligible studies are included, the following two steps will prioritize the extraction process:

1. Extract only studies with >500 patients that report on all-cause mortality, or with >100 patients reporting on other outcomes. As we expect to find many studies reporting all-cause mortality, not necessarily related to anticoagulation or thrombosis, we will prioritize larger studies.
2. Extract in the following order of importance:
   - All Incidence rate studies for prioritized outcomes (baseline risk) that provide details on thromboprophylaxis strategies
   - Prognostic factors for first-time VTE
   - Incidence rate studies for prioritized outcomes (baseline risk) that do not provide details on thromboprophylaxis strategies
   - Prognostic factors for all-cause mortality
   - Prognostic factors for remaining prioritized outcomes

If not enough time in Phase 1, prognostic factor evidence for non-VTE outcomes will be extracted in Phase 2.

Risk of bias assessment

Risk of bias will be assessed using the Quality in Prognosis Studies (QUIPS) tool.[13] The complete tool will be used to assess risk of bias for the association of risk factors with outcomes of interest, using either a cohort or case-control design. The domains of 'Prognostic factor measurement', 'Study confounding' and 'Statistical analysis reporting' will not be assessed for evidence on incidence rate or cumulative incidence (research question #1) as they are not applicable. For both, an overall judgment for risk of bias will be made. The Prediction Study Risk of Bias Assessment Tool (PROBAST) tool will be used to assess risk of bias for risk assessment models.[14]

In the Phase I initial review, studies will be assessed by one person and uncertainties verified by a senior team member (HS or RN). 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 (HS or RN). 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: 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)

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 incidence or prognostic risk factors. 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).

Incidence (research question #1)

Risk of outcomes will be reported as incidence rate per unit of follow-up time, and/or cumulative incidence over a fixed follow-up duration for the whole population. Where possible and deemed appropriate, we will calculate pooled outcome incidence with a measure of dispersion (e.g., 95% confidence interval or interquartile range). Cumulative incidence may be transformed to incidence rate and pooled as such, only when we can assume for the cumulative incidence that: 1) the event is likely to occur only once in each person; 2) everyone had the same follow-up time; 3) and for non-mortality events where mortality may be a competing event, that mortality is low enough to assume the same follow-up time. As some events may have a very low incidence rate, we will pool data using a generalized linear mixed effects model (GLMM) that allows inclusion of studies with no events without a continuity correction.[16] GLMM will also allow adjusting for thromboprophylaxis administration or dosing, as dichotomous or continuous variable. If feasibility, poor reporting, or data distribution precludes pooling of studies, a range of incidence estimates will be reported.

Prognostic factors and models (research question #2)

For measures of association regarding risk factors, we will present unadjusted and adjusted estimates separately. If multiple studies report on the same risk factor and pooling is considered feasible and appropriate, we will calculate a pooled measure of association. Different types of measures will be pooled separately (RR, OR, HR). Only if the event rates are low, and we can assume that the risk for the outcome stays consistent over the follow-up time period with the same follow-up duration in all patients (minimal censoring), we will consider pooling different measures of association. If no adjusted measures of association are reported, we will consider using meta-regression analysis to adjust for study-level variables, if possible.

Prognostic (risk assessment) models will be described narratively, and results for their individual risk factors will be integrated with the risk factor analysis above, if possible.

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: prospective cohort vs. retrospective cohort (vs case-control for risk factors)
- Geographic region: different countries
- Study size: studies with fewer than 5 outcome events vs. studies with 5 or more outcome events
- If relevant:
    - Unpublished/preprint vs. peer-reviewed publications
    - RCT vs observational

Subgroup analysis

Heterogeneity will be explored using subgroup analyses, which can include type or dose of thromboprophylaxis, severity of COVID-19, among others. In addition, we will separately analyze pooled estimates for studies only reporting on COVID-19 patients with a specific comorbidity.

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