Scientific Advisory Group

COVID-19 Scientific Advisory Group Rapid Evidence Brief

Evidence for screening and preventing venous thromboembolic events in patients with COVID-19 [UPDATED]

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Alberta Health Services

Physical distancing works

Table of contents

Lay Summary

BACKGROUND

- Patients who are hospitalized with COVID-19 are at high risk for abnormal blood clot formation, called deep vein thrombosis, and clots starting in or travelling into the circulation of the lungs (called pulmonary thromboembolism). Together these are referred to as venous thromboembolism (VTE), and these complications can occur even when patients have been given “blood thinner” medications to try to prevent abnormal clotting.
- Knowledge of how best to manage or prevent COVID-19 complications is constantly changing and the research in this area has been very fast moving, leading to possible differences in care practices across Alberta. As well, there have been different recommendations around which hospitalized COVID-19 patients should have blood tests (D-dimer testing), ultrasounds or CT scans to look for these complications and what dose of blood thinners should be given based on the changing literature.
- This review summarizes the medical literature of best practices in these areas (randomized controlled trials, systematic reviews, meta-analyses, and guidelines) to provide guidance on best practices for use of blood thinners and VTE prevention to our medical teams looking after hospitalized patients with COVID-19.

KEY MESSAGES

- Hospitalized patients with COVID-19 are at increased risk for VTE.
- The blood D-dimer test is often elevated in COVID-19 patients even without VTE, therefore it is not always helpful on its own in assessing for VTE, but the degree of elevation is associated with vascular thrombosis and poor clinical outcomes. D-dimer greater than two times the normal limit is a predictor of VTE in COVID-19 patients and if associated with **unexplained increasing oxygen requirements** should prompt consideration for investigation for diagnosis of VTE (ultrasound doppler of lower extremities for DVT and/or CTPE for pulmonary embolism).
- North American guidelines recommend against universal screening for VTE in all COVID-19 patients, and suggest that patients at highest risk of VTE based on clinical risk assessment and with possible VTE symptoms should have leg ultrasound or chest CT imaging to look for DVT/PE.
- Hospitalized patients with COVID-19 can have significant inflammation, with blood clots in small and larger blood vessels leading to poor clinical outcomes. In those presenting to hospital with moderate sickness (needing low flow oxygen), full dose blood thinners may result in increased chance of survival to hospital discharge without the need for ICU-level organ support.
- On the contrary, in critically ill COVID-19 patients (on high flow oxygen or other forms of organ support), introducing full dose blood thinners did not lead to lower mortality or less need for ICU-level of organ support. Research suggests that full dose blood thinners may cause more harm in critically ill patients because of the increased bleeding risk.
- Research into VTE prophylaxis is ongoing and guidance may change in the future.

RECOMMENDATIONS

1) Prevention of worse clinical outcomes (need for organ support, ICU-level care and death):

   In moderately sick hospitalized COVID-19 patients on low flow oxygen, full dose blood thinners with heparin (LMWH preferred) can be considered in patients with low bleeding risk, for 14 days or until discharge (whichever is less), as this may improve patient survival until hospital discharge without the need for ICU-level organ support.

2) In critically ill hospitalized COVID-19 patients with no contra-indications to blood thinners, prevention dose blood thinners are suggested over full dose blood thinners.
   a. Critically ill is defined as: Hospitalized patients requiring ICU-level organ support (high flow rates of oxygen for breathing support, mechanical ventilation, other machines that support the heart and lungs and or kidneys outside of the body, medications for blood pressure support).
   b. In patients who have progressed from moderate to critically ill, we suggest continuing full dose blood thinners if started at admission.
   c. In patients who are transitioned out of ICU to a medical ward, we suggest leaving them on prevention dose blood thinners for the duration of the hospitalization.

3) Prevention of blood clots:
   a. All patients with COVID-19 infection admitted to hospital (who do not meet criteria for full dose blood thinners; see 1) should still be provided preventative dosing of blood thinners, unless contraindicated.
   b. Hospitalized patients with COVID-19 who have high bleeding risk or other medical reasons that prevent them from using blood thinners should receive mechanical prevention with special compression stockings for their legs until their bleeding risk subsides. After bleeding risk has gone down they should be given preventative doses of blood thinners for the remainder of the hospitalization.
   c. Post-discharge preventative blood thinners are not recommended, based on current evidence.
   d. Studies are continuing in this area and recommendations may change in the future.

4) Diagnosis of blood clots:
   a. A blood test called the D-dimer can identify patients who have a higher level of clotting activity. Levels that are measured as more than twice the normal level are predictors of clotting in COVID-19 patients. Patients found to have a D-dimer greater than or equal to twice the normal level and increasing oxygen requirements without a change in their x-ray findings, should be considered for tests to rule out a blood clot in their lungs. If testing is not available on a timely basis and the patient is at low risk for bleeding, they should also be considered for full dosage blood thinners until a clot can be ruled out.
   b. Further testing should be done if there are signs or symptoms suspicious for a blood clot (such as unexplained high heart rate, low blood pressure, one sided leg swelling, or chest pain).
   c. Routine testing for VTE without symptoms or signs of clotting is not recommended.

Authorship and Committee Members

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Topic: Risk stratification, Screening and Prevention of VTE in COVID-19

1. Risk of VTE
    - Is there evidence of increased risk of DVT/PTE in COVID-19 patients? What patient factors are associated with increased risk?

2. Screening and diagnosis of VTE
    - Should all, or only select high risk groups, patients with COVID-19 be screened for DVT/PE?
    - What testing should be done to support diagnosis of DVT/PE in these groups of COVID-19 patients?
    - What is the significance of a positive D-dimer in patients with COVID-19?
    - What is the utility of bilateral lower limb ultrasound screening in patients without clinical features suggesting VTE?

3. Prevention of VTE
    - Is VTE prophylaxis safe and effective for COVID-19 patients? Is prophylaxis recommended for all COVID-19 patients, or for specific groups of COVID-19 patients?

4. Prevention of organ support and ICU-level care
    - Does therapeutic anticoagulation confer additional clinical benefit over prophylactic anticoagulation in specific groups of hospitalized COVID-19 patients?

Context

- COVID-19 cases in Alberta are rising with increased hospitalizations requiring the formation of COVID wards staffed by physicians recruited from all specialties.
- Hospitalized patients are at increased risk for venous thromboembolic complications such as deep vein thrombosis or pulmonary embolism. Prophylaxis of venous thromboembolism in hospitalized medical patients, with low-molecular weight heparin, unfractionated heparin, or mechanical compression is standard of care.
- Despite the routine use of thromboprophylaxis, a higher prevalence of VTE has been identified in patients hospitalized with COVID-19. Despite recognition of increased risk, there is a lack of guidance regarding the screening, diagnosis, and prophylaxis of venous thromboembolism in COVID-19 patients; further, emerging evidence on anticoagulation to improve other clinically important outcomes is now available.
- The information in this review is a summary of available evidence-based guidelines and systematic reviews intended for use by frontline physicians providing care for patients hospitalized with COVID-19

Key Messages from the Evidence Summary

1. Is there evidence of increased risk of DVT/PTE in COVID-19 patients? What patient factors are associated with increased risk?
    - All hospitalized patients with COVID-19 are at high risk of VTE events (pooled incidence 25%, CI 19 -31%, with higher event rate of PE vs DVT of 19% vs 7%, respectively) and should be treated with at least usual dosages of pharmacological thromboprophylaxis with LMWH, if not therapeutic doses in non-critically ill patients (see #4)
    - Patients with COVID-19 who are at a particularly higher risk include: those with more severe disease, those in the ICU, requiring mechanical ventilation as well as patients with the traditional risk factors for VTE including male gender, prior VTE, active cancer and obesity.

2a. Should all or only select high risk groups of patients with COVID-19 be screened for DVT/PE?

- Traditional signs and symptoms of DVT or PE (VTE) should be used to guide further investigations.

2b. What testing should be done to support diagnosis of DVT/PE in these groups of COVID-19 patients?

- Compression duplex ultrasonography and computed tomography (with PE protocol) remain the diagnostic standards for DVT and PE, respectively.

2c. What is the significance of a positive D-dimer in patients with COVID-19?

- D-dimer levels are frequently elevated in patients with COVID-19 and are felt to be secondary to sepsis, inflammation and clotting activity; the clinical significance of elevated D-dimer levels is of uncertain clinical significance in this setting.
- Elevated D-dimer levels are not specific for VTE and should not be used solely to guide further investigations or management.
- A D-dimer level greater than twice the upper limit of normal is associated with VTE and elevated D-dimer levels are also associated with a higher mortality in COVID-19 hospitalized patients

2d. What is the utility of bilateral lower limb ultrasound screening in patients without clinical features suggesting VTE?

- The use of routine screening by bedside ultrasonography identifies additional VTE cases, however the clinical implications of ultrasound screening, such as the benefit of treating asymptomatic distal VTE, are currently unknown in the COVID-19 population.

3. Is VTE prophylaxis safe and effective for COVID-19 patients? Is prophylaxis recommended for all COVID-19 patients, or for specific groups of COVID-19 patients?

- There are many ongoing randomized controlled trials comparing different therapies for VTE prophylaxis in hospitalized COVID-19 patients.

- Retrospective cohort studies show that the use of usual dosages of pharmacological VTE prophylaxis reduces the risk of VTE in COVID-19 patients but does not eliminate all risk of VTE events.
- Low or variable use of VTE prophylaxis in a number of early COVID-19 cohort studies from Asia or parts of Europe limits the assessment of the effectiveness of standard VTE prophylaxis in this population and do not reflect standard care in North America.
- See below for discussion of evidence on use of intensified pharmacological thromboprophylaxis in certain groups of patients with COVID-19
- All guidelines identified in our review were published before the announcement that the above trials have stopped recruitment of critically ill patients.

4. Does therapeutic anticoagulation confer additional clinical benefit over prophylactic anticoagulation in specific groups of hospitalized COVID-19 patients?

- Therapeutic anticoagulation in hospitalized, moderately ill, COVID-19 patients at low risk for bleeding may increase the probability of survival until hospital discharge without the need for ICU-level organ support at 21 days compared with usual thromboprophylaxis.
- For every 1000 hospitalized COVID-19 patients with non-ICU level care and low risk of bleeding, therapeutic anticoagulation may result in the survival of 40 additional patients until hospital discharge without organ support at the expense of seven additional major bleeding events (based on the multiplatform trials (ATTACC/ACTIV-4a/REMAP-CAP) (48))

Committee Discussion

The committee in general were supportive of the revision with the inclusion of RCT evidence from the multiplatform trials showing benefit for therapeutic anticoagulation in moderately ill COVID-19 patients in distinction from critically ill COVID-19 patients. They discussed the need for clarity surrounding the classification of 'moderately ill' versus 'critically ill' COVID-19 patients favoring level of oxygenation and/or other forms of organ support as opposed to “ICU setting” given the fluid nature of ICU bed capacity and timing of admission or transfer. The definition of high flow nasal cannula that was used in the studies as the cut off for moderate COVID-19 was variable but based on the criteria used in the multiplatform trials and RAPID COVID-COAG the use of low flow oxygen or a level of less than 30 litres/min was chosen over an FI02 level. The newer inclusion of an outcome of survival to discharge without organ support was felt to be distinct from VTE related outcomes; the importance of the timing of initiation of anticoagulation in the trajectory of the hospitalization was also discussed.

Increased bleeding risk, especially in the critically ill population, was highlighted as an important factor in determining who would be considered a candidate for therapeutic anticoagulation to avoid net harm. While HASBLED had been identified as a simple and validated tool for identifying hospitalized patients at higher risk for major bleeding, several reviewers cautioned that it was not intended or studied prospectively in patients with COVID-19. A retrospective study by Yu et al, (57) did identify a HASBLED of 3 as a

predictor of major bleeding in a study of 973 hospitalized COVID-19 patients. Using usual contraindications to anticoagulation and criteria for exclusion from the trials was felt by some reviewers to not identify all of the bleeding risk identified in the studies. Alternatives to HASBLED including the IMPROVE bleeding risk assessment tool (55) or the RIETE score for bleeding risk associated with PE (56) were considered but have minimal evidence in the COVID-19 population. The identified bleeding risk factors from the trials were included in the current revision and specific bleeding risk scores such as HASBLED were removed from the recommendations.

Several reviewers cited more recent guidelines, including ASH, Ontario Science Table and BC Health to have suggested a more cautious approach to the use of therapeutic anticoagulation to capture the need for more robust data and outcomes and to allow for better individual patient risk- benefit assessment. While a number of these groups have not had an opportunity to adequately review the now published multiplatform trial data, ASH did include in its FAQ the following recommendation pending the updated guideline:

'Based on these still evolving data we advise that moderately ill patients be carefully considered for therapeutic dose anticoagulation with a determination of individual net clinical benefit in the absence of objectively confirmed VTE.'

Several reviewers commented on the importance of identifying a subgroup that are more likely to benefit with this modest improvement in outcomes that is associated with some increased risk of major bleeding. While the multiplatform trials did show benefit across all D-dimer groups, there was a substantial increase in benefit for those with D-dimer > 2x ULN. Additional discussion around indications for testing for VTE and duration of therapy for prophylaxis and treatment dosages of anticoagulation were included in the revision.

Further discussion around the appropriateness of a 'recommendation' versus 'suggestion', occurred. There was consensus that the inclusion of multiple RCTs in the form of a high quality, multiplatform trial, including more than 1000 patients with a clinically important outcome was a strength of the evidence. However, the effect size in the study was small, and since the conduct of this trial other effective treatments are now used; it is not known whether benefit with anticoagulation would be seen when provided in addition to the other changes in care that have occurred. With input from the committee, it was determined that instead of stating ‘recommend’, it should be framed as 'can consider'. Details around the definition of 'moderately-ill' COVID-19 patients and the classification of 'low risk of bleeding' were felt to be more appropriate for practical considerations.

Finally, the infographic was discussed as a good way to summarize and communicate the important aspects of this review and support earlier translation to frontline health care teams and will be revised to include the key changes.

Recommendations

Recommendation 1: Considering evidence from RCTs examining the use of therapeutic anticoagulation for preventing adverse clinical outcomes (including need for organ support, ICU-level care or death):

a. In hospitalized COVID-19 patients on low flow oxygen, therapeutic anticoagulation with heparin with preference for LMWH (for example, Tinzaparin 175u/Kg SC daily) can be considered in patients at low bleeding risk, for 14 days or until discharge (whichever is less), as this may increase the probability of survival until hospital discharge without the need for ICU-level organ support. Those with D-dimer more than 2X ULN may be more likely to benefit. Prevention dose anticoagulation should be offered to all patients not on therapeutic dose, to reduce the risk of thrombosis.
b. In critically ill hospitalized COVID-19 patients with no contra-indications to anticoagulation, weight based prophylactic anticoagulation is suggested (e.g., Tinzaparin 75u/Kg SC daily) over therapeutic dosing. This would include patients requiring high flow oxygen and those requiring non-invasive or invasive mechanical ventilation, extracorporeal life support, vasopressor or inotropes.
c. In patients who progress from moderate to critical illness while on full dosage anticoagulation, we suggest continuing therapeutic anticoagulation.
d. In patients who are transitioned out of ICU to ward, we suggest leaving them on the weight based DVT prophylaxis or if on therapeutic dosing to retain the latter for the duration of the hospitalization.

Rationale: This recommendation is made to help increase the number of patients who survive to discharge without requiring organ support in the ICU. Multiple studies have not demonstrated benefit in therapeutic anticoagulation for critically ill patients in the ICU in the absence of VTE diagnosis. In the moderate severity COVID-19 patients, the multiplatform trials (ATTACC, ACTIV-4a & REMAP-CAP) demonstrated increased probability of survival until hospital discharge without the need for ICU-level organ support at 21 days as compared to standard thromboprophylaxis (48); however the effect size was small and there remains uncertainty in this evidence.

Recommendation 2: Considering evidence from RCTs examining the use of anticoagulation for prevention of VTE:

a. All patients with COVID-19 infection admitted to hospital should be provided venous thromboembolism prophylaxis, unless contraindicated.
    i) Literature specific to prevention of VTE with higher than usual preventative doses of anticoagulation has been mixed based on the presence of risk factors for VTE. The recent HEP-COVID trial demonstrated reduced incidence of the combined incidence of VTE, ATE (arterial thromboembolism) or death (but heavily weighted to the reduction in VTE) with therapeutic dose anticoagulation for non-ICU stratum and D-dimer 4X ULN, with no significant difference in bleeding between the two groups.
b. In non-critically ill COVID-19 patients who have a high bleeding risk including those with prior major hemorrhage or severe kidney disease we recommend continuing with weight-based prophylaxis with LMWH for the duration of their hospitalization.

c. In hospitalized COVID-19 patients with a contraindication to prophylactic anticoagulation, we recommend the use of mechanical prophylaxis with pneumatic compression stockings with a plan to review the need for pharmacologic prophylaxis once the bleeding risk has resolved.

Rationale: Multiple cohort studies and some moderate quality meta-analyses or systematic reviews have demonstrated the high-risk of VTE in this population, warranting the use of pharmacologic thromboprophylaxis. Prophylactic dosage LMWH has been found to reduce the risk of VTE in medical patients and in COVID-19 patients and to be associated with a low risk of major bleeding. There is no evidence of effectiveness of prophylactic dosage DOACs in this population and some evidence of increased risk of bleeding, especially in context of risk of AKI and multiple drug interactions with critically ill patients with COVID-19. Studies are continuing in this area and recommendations may change in the future.

Recommendation 3: Considering evidence around diagnosis of VTE:

a. Given an increased risk of VTE associated with COVID-19, patients admitted with COVID pneumonia could be considered for additional testing to rule out VTE in the presence of additional signs and symptoms.
    - This includes those with unexplained hypoxia without significant chest X ray abnormalities or a worsening of CXR abnormalities especially in the presence of a D-dimer level greater than 2 x the ULN.
    - Having a D-dimer result >=1 mg/l or greater than 2x the ULN in people with additional VTE risk factors or indicators such as signs or symptoms of VTE is associated with a high sensitivity and specificity for a diagnosis of PE.
b. If unable to get CTPE on a timely basis and low risk for bleeding, patients should also be considered for therapeutic dosage low molecular weight heparin until this can be ruled out.
c. Routine screening for VTE in hospitalized COVID-19 patients is not recommended.

Rationale: It is currently unknown whether there is clinical benefit to treating clinically silent VTE events identified on universal screening and there could be increased bleeding risk.

Recommendation 4: Considering current evidence for post-discharge thromboprophylaxis, extended post-discharge pharmacological thromboprophylaxis is not recommended.

Rationale: RCTs of Extended LMWH or DOAC prophylaxis for medical patients admitted with severe respiratory disease, MI, CHF, cancer or sepsis did not show evidence of significant benefit and some evidence of harm secondary to increased bleeding rates. Clinical trials of extended thromboprophylaxis in higher risk COVID-19 patients are underway, which will inform future recommendations.

Summary table: Intersection of recommendations and practical considerations at a patient level

Severity of Illness at hospital admission	Bleeding risk	Suggested Anticoagulation therapy
Moderately ill COVID-19 patients (on low flow oxygen by nasal cannula and not in ICU)	Low	Therapeutic anticoagulation with LMWH (e.g., Tinzaparin 175u/Kg SC daily) is recommended for 14 days or until discharge (whichever is shorter).
	High	Weight-based prophylactic-intensity LMWH is suggested over therapeutic intensity in patients with high bleeding risk (e.g., tinzaparin 75u/Kg SC daily). If contra-indicated, mechanical thromboprophylaxis is suggested over no prophylaxis.
Patients with Moderate progressing to critically ill COVID-19 infections	Low	Continue with therapeutic anticoagulation (e.g., Tinzaparin 175 u/kg sc daily) unless new contraindication develops.
	High	Continue with weight-based prophylactic intensity LMWH. If contraindication develops, mechanical thromboprophylaxis is suggested until this resolves.
Critically ill COVID-19 patients requiring oxygen delivered through high flow nasal cannula, non-invasive or invasive mechanical ventilation, extracorporeal life support, vasopressors, or inotropes).	Low	Weight-based prophylactic-intensity LMWH is suggested over therapeutic dosing. (e.g., tinzaparin 75u/Kg SC daily).
	High	Weight-based prophylactic-intensity LMWH is still suggested over no anticoagulation (e.g., tinzaparin 75u/Kg SC daily), unless contraindicated. If contra-indicated, mechanical thromboprophylaxis is suggested over no prophylaxis.
Hospitalized COVID-19 patients found to have a VTE event at admission or despite VTE prophylaxis	Low or High Bleeding Risk	Therapeutic anticoagulation with weight-based LMWH (e.g., Tinzaparin 175 u/kg SC daily) (If contraindicated and significant DVT clot burden, consider for IVC filter until contraindication resolves.)

		Treatment considered for at least 3 months or resolution as a provoked VTE

Practical Considerations

- Maintain a high clinical suspicion for venous thromboembolism.
- Diagnostic imaging such as ultrasonography may be performed at the bedside in the critical care setting, if feasible, to minimize transport and limit potential COVID-19 exposure to healthcare workers.
- Choose a heparin-based (LMWH preferred) regimen that minimizes the number of interactions with COVID-19 patients. In Alberta, this would suggest standard prophylaxis dosing of tinzaparin 75u/kg (e.g., once daily injections) for the duration of the hospitalization.
- Assessing bleeding risk:
    - Patients at high risk of bleeding were excluded from the multiplatform trials, which included patients with: age 75 or greater, eGFR less than 30 mL/min, any coagulopathy, platelet count less than 50, use of dual antiplatelet therapy, recent history of serious GI bleed or recent intracranial condition (stroke, neurosurgery, aneurysm, cancer), epidural or spinal catheter.
    - In addition to the risk factors above, bleeding risk assessments tools such as HASBLED, IMPROVE and RIETE may help clinicians risk stratify patients at admission and to support documentation and communication of that risk at transitions in care (55-57). A HASBLED score of 3 or more has been identified as a predictor of COVID-19 patients with an increased risk of major bleeding in at least one cohort study of more than 930 COVID-19 patients (57).
- The current multiplatform trials of therapeutic anticoagulation identified a statistically significant improvement in survival to discharge without the need for organ support for moderately ill COVID-19 patients treated within 72 hours of admission. While the classification of 'moderately-ill' included patients who were not on high flow oxygen (less than 30 l/min or FIO2 40%), the majority of the patients included were presenting with acute respiratory illness and were on low flow oxygen. Critically ill COVID-19 patients including those on high flow oxygen, or non-invasive ventilation did not garner any benefit from therapeutic anticoagulation and had higher risk of major bleeding including a signal of overall worse outcomes. This would suggest that those presenting who are already above the 6 l/min low flow oxygen threshold may not achieve the same benefit from therapeutic anticoagulation. In this case, further attention to the presence of additional risk factors for VTE or bleeding should be sought before considering for therapeutic anticoagulation.
- While the benefit of therapeutic anticoagulation for moderately ill COVID-19 patients was found to be present for patients with a D-dimer less than or greater than 2 x the ULN and in those without a D-dimer, the benefit was strongest in those with a D-dimer of at least 2x ULN. D-dimer, as well as assessment for

additional risk factors for VTE should be included in the risk assessment at admission to support the risk-benefit discussion before initiating therapeutic anticoagulation.
- It may be reasonable to consider pharmacological thromboprophylaxis in acutely ill COVID-19 infected patients who are hospitalized for other indications or not hospitalized (but would otherwise have fit criteria for hospitalization), especially if they have risk factors for VTE such as immobilization, active malignancy, obesity, etc. (see Research Gaps). This would include residents of Long Term Care facilities who are being treated in place for COVID-19 infection. The increased risk of VTE is associated with patient and disease factors, not their environment.

Research Gaps

- There is an abundance of observational data that demonstrated that patients admitted with COVID-19 are at higher risk of VTE and in particular pulmonary embolism, with a suggestion that immunothrombosis associated with COVID-19 may account for this increased VTE rate, and the possible decreased effectiveness of pharmacological thromboprophylaxis in modifying risk. Further pathophysiological investigations are required.
- Studies focused on the VTE risk assessment and optimal diagnosis and management of VTE risk in outpatients or acutely ill non-hospitalized patients with COVID-19 are lacking.
- Overall, there is a paucity of high-quality studies examining the optimal diagnostic and therapeutic strategy to identify and prevent VTE in COVID-19 patients.

Strength of Evidence

- Meta-analysis and systematic reviews of the prevalence of VTE from multiple retrospective cohort studies are moderately robust, demonstrating consistent results that the prevalence of VTE and in particular, pulmonary embolism, is higher than expected among patients with COVID-19 and especially high in those with severe COVID-19 infections requiring admission to ICU and mechanical ventilation.
- Recommendations regarding optimal prophylactic anticoagulation regimens in COVID-19 patients is now based on randomized controlled trial data

Limitations of this review

- This rapid review is based on current narrative reviews, meta-analysis, guidelines and positions statements. As a result, recently published clinical trials may have been missed.
- Due to the novel nature of COVID-19, many included studies are based on small sample sizes and include heterogeneous populations. However, there are a few randomized controlled trials that have robust sample sizes with more than 1000 patients, including the multiplatform trials (48).

Summary of Evidence

Research Question 1 – Risk of VTE

a) Is there evidence of increased risk of DVT/PE in COVID-19 patients?

- Several systematic review and meta-analysis of observational data have demonstrated that patients admitted to hospital with COVID-19 have a high prevalence of VTE (25%, 95% CI, 19–31%); with or without prophylactic dose thromboprophylaxis (1-7). This is approximately double the rate usually reported for hospitalized medical patients.
- In all populations, patients admitted with COVID-19 demonstrated an increased prevalence of PE (19%; 95% CI, 13–25%) relative to DVT (7%; 95% CI, 4–10% (1, 2, 4, 7-9). The variability in these estimates is due to differences in screening strategies, definitions of thrombotic events and inclusion of population of patients with different severity of illness.
- The overall prevalence of VTE was generally higher among patients in the ICU setting (17-31%) compared to those admitted to a hospital ward (7-31%) and with patients with more severe COVID-19 infections. (4-8, 10).

b) What patient factors are associated with increased risk?

- Among non-COVID-19 patients treated in the ICU, general risk factors for VTE include advanced age, prior VTE, history of cancer, prolonged immobilization, obesity, pregnancy, trauma, spinal cord injury, recent surgery, and stroke (11)
- Patients with a severe illness (any of: respiratory rate >30, SpO2 <93%, PaO2/FiO2 <300 or >50% lung infiltrates) have demonstrated a higher incidence of VTE compared to patients without severe illness (35% versus 6%; relative risk 4.76; 95% CI 2.66-8.50)(1).
- In addition to traditional risk factors for VTE, **increased age and BMI** have been identified as independent risk factors for VTE in the setting of COVID-19 (5).
- Several risk factors including D-dimer > 1-3 mg/l, ICU admission, and mechanical ventilation were also frequently reported independent predictors for the development of thrombotic events (12).

Synthesis of the Information Relating to Question 1

- Despite the use of traditional VTE prophylaxis, patients with COVID-19 are at a high risk of VTE due to a profound systemic inflammatory response and resultant hypercoagulability. Patients with COVID-19 share traditional risk factors for VTE as outlined by the Padua score, including advanced age, prior history of VTE, history of active malignancy, prolonged immobilization, acute infection, and obesity (13).

Research Question 2 – Screening for VTE

a) Should all, or only select high risk groups of COVID-19 patients be screened for DVT/PE?

- Due to reduced specificity of D-dimer in patients with COVID-19, The European Society of Cardiology suggests that only traditional signs and symptoms of a pulmonary embolism should trigger further investigations(14). These include:
    - Unexpected respiratory worsening
    - New/unexplained tachycardia,
    - A fall in blood pressure not attributable to tachyarrhythmia, hypovolemia or sepsis,
    - New electrocardiographic changes suggestive of PE and
    - Signs of deep vein thrombosis of the extremities
- The Society of Thrombosis and Hemostasis Research adds that a rapid increase in D-dimer levels should prompt further investigation for VTE, however this based on expert opinion (15).
- The suspicion of PE should be based in clinical grounds (unexplained chest pain, unexplained RV dysfunction, unilateral lower limb swelling) and not only in biomarkers such as D-dimers. It is known that D-dimers are frequently high in COVID-19 inpatients, and may be indicative of severe disease, but it is not clear if they reflect the existence of macrovascular thrombosis and/or the need to screen systematically VTE in these patients unless additional risk factors or signs are present (16).

b) What testing should be done to support diagnosis of DVT/PE COVID-19 patients?

- In addition to traditional diagnostic investigations, no novel radiographic or biomarker tests have been identified that reliably aid in the diagnosis of VTE in patients with COVID-19.
- Traditional evaluation for VTE with duplex ultrasound or CT should be undertaken based on clinical suspicion for VTE and not solely on D-dimer levels(17).
- The American College of Radiology suggests that ventilation/perfusion scans be avoided if possible due to possible risk of exposure of COVID-19 to technicians and patients (18).

c) What is the significance of a positive D-dimer in patients with COVID-19?

- Although elevated D-dimer levels are frequently associated with more severe cases of COVID-19 (19), it is unclear if it can be used to diagnose or predict risk of VTE.
- A large meta-analysis has demonstrated that there is no independent association between D-dimer levels and VTE (3).
- However, additional studies have demonstrated that in the ICU setting a D-dimer level of >1.5 mg/l had an 85% sensitivity, 88.5% specificity and negative predictive value of 94.7% for detecting VTE (20). A D-dimer level >1 mg/l was found to have a high sensitivity (91%) but very low specificity (24%) (8).
- A study of 443 patients with COVID-19 admitted to a hospital in Switzerland identified a 9% risk of VTE with a 3.2% risk of VTE on presentation with 2/3 PE

and 1/3 DVT. A D-dimer > 1 mg/l or a Wells score > or = to 2 provided a sensitivity of 93% but specificity of 47% while a D-dimer of 3 mg/l and a Wells score of greater than or equal to 2 provided a sensitivity of 57% but specificity of 93% for PE on admission to hospital. They identified a presentation at or later than 8 days of illness was also a predictor of VTE on admission (47).

d) What is the utility of bilateral lower limb Doppler ultrasound screening in patients without clinical features suggesting VTE?

- In a small case series of 34 patients admitted to the ICU with severe COVID-19 treated with usual thromboprophylaxis, the use of routine lower limb ultrasound 48 hours after admission identified DVT in 79% of asymptomatic patients(21). A meta-analysis of routine use of Doppler ultrasound cases in an unselected population demonstrated that this approach identifies a higher prevalence of VTE (40.3%), suggesting a high burden of undiagnosed VTE in patients admitted with COVID-19 (22). However, the impact of universal screening in either hospitalized patients or ICU patients on clinical outcomes has not been assessed.
- A systematic review of ten studies which performed screening ultrasonography for DVT in all patients found a DVT incidence between 0 and 85% and seemed to be largely accounted for by asymptomatic distal DVT. The incidence of bleeding complications in these studies ranged from 0 and 10.6% (23).
- The CHEST guidelines recommends against routine screening for hospitalized and critically ill patients, but suggest a lower threshold for performing investigatory tests for VTE due to the high prevalence of VTE in this population (24).

Synthesis of the Information Relating to Question 2

- While systematic screening of patients with COVID-19 does identify a higher prevalence of VTE, many of these are clinically silent distal DVTs and of uncertain clinical significance. No studies have evaluated whether universal screening for VTE is associated with improved clinical outcomes. The use of D-dimer alone should not be used to guide further investigations, due to the reduced specificity in the COVID-19 population. Traditional signs and symptoms for VTE should be used to guide further investigations such as CTA, duplex compression ultrasonography, and if necessary, V/Q imaging.

Research Question 3 – Thromboprophylaxis

Is VTE prophylaxis safe and effective for COVID-19 patients? Is prophylaxis recommended for all COVID-19 patients, or for specific groups of COVID-19 patients?

Traditional VTE prophylaxis

- In a meta-analysis of 17 retrospective studies examining VTE rates in COVID-19 patients, studies reporting a high use of thromboprophylaxis >60% demonstrated a reduced rates of VTE compared to those with a lower rate of thromboprophylaxis rate (19% versus 40%) (1).

- In patients with a sepsis-induced coagulopathy (SIC) score of four or greater or a D-dimer 6x above the upper limit of normal, thromboprophylaxis was associated with a reduction in 28-day mortality (25).
- A meta-analysis of all patients hospitalized with COVID-19 demonstrated that the overall major bleeding rate was 4.7% in those receiving standard VTE prophylaxis dosing LMWH. In patients treated with intermediate or full-dose anticoagulation the major bleeding rate was significantly higher at 21.4% (7).
- The CHEST guideline recommends daily LMWH and fondaparinux over UFH to limit staff exposure. They also recommend current standard dose anticoagulant thromboprophylaxis (Table 3) over intermediate dosing or full dosing in hospitalized and critically ill patients due to insufficient data to justify increased intensity thromboprophylaxis (26).
- The CHEST guideline recommends against the combination of mechanical with pharmacological thromboprophylaxis (26).

Intensified VTE prophylaxis - studies

- The HEP-COVID trial showed a reduction in their primary outcome of venous thromboembolism, arterial thromboembolism or death from any cause within 30 days of randomization in non-ICU patients who received therapeutic anticoagulation, compared with usual-care pharmacological thromboprophylaxis. This was primarily driven by a reduction in VTE. This effect was not seen in the ICU population (51).
- The ACTION trial demonstrated no difference in the combined outcome of death, duration of hospitalization or duration of supplemental oxygen to 30 days in patients on therapeutic anticoagulation versus pharmacological thromboprophylaxis (using DOACs). There was also no difference in the secondary outcome of thrombotic events between the two groups (49).
- In a study by Perepu US et al, intermediate dose anticoagulation did not demonstrate superiority over pharmacological thromboprophylaxis in terms of reducing death or thrombosis at 30 days, and no significant excess minor or major bleeding was observed (50).
- INSPIRATION did not demonstrate any significant difference in the primary outcome of venous/arterial thrombosis, ECMO requirement, or mortality within 30 days in ICU patients who received intermediate dose thromboprophylaxis vs standard dose thromboprophylaxis (52).
- RAPID COVID-COAG, a randomized controlled, adaptive, open label clinical trial of therapeutic heparin compared with prophylactic heparin among 465 moderately ill patients with COVID-19 admitted to hospital wards, did not demonstrate any significant difference in the primary outcome including the composite of ICU admission, non-invasive (bi-level or continuous positive airway pressure) or invasive mechanical ventilation, or death up to 28 days. While they did not have power to rule out the primary income or VTE events overall, the odds of death at 28 days was decreased and the risk of major bleeding appeared low (54).

- A small RCT of 20 patients with severe COVID-19 infection requiring mechanical ventilation were randomized to either prophylactic of therapeutic doses of enoxaparin.
    - In this small trial, patients in the therapeutic dose arm demonstrated improvement in PaO2/FiO2 ratio, higher rates of successful extubation and more ventilator-free days (29).
- In a retrospective cohort of 2,773 patients hospitalized with COVID-19, the use of therapeutic dose anticoagulation in-hospital (n=786) was associated with improved in-hospital survival, in particular in patients requiring mechanical ventilation (30).
    - However, this study is severely limited by its observational nature and unknown indications for anticoagulation. This risk of major bleeding in patients on therapeutic anticoagulation was 3% compared to 1.9% in patients who did not receive therapeutic anticoagulation.
- A similar observational study of 279 patients with COVID-19 requiring mechanical ventilation demonstrated that patients receiving therapeutic anticoagulation (n=161) exhibited improved 35-day survival rates compared to patients receiving prophylactic anticoagulation (58% versus 14%) (31).
    - However, again this study is limited by its observational nature and inability to assess for confounding factors.

Intensified VTE prophylaxis - guidelines

- In the CHEST guidelines, intensified VTE prophylaxis (e.g. intermediate, half-therapeutic LMWH dosage once daily or with a high-risk prophylactic LMWH dosages twice daily) has been recommended in patients with additional risk factors (e.g. BMI > 30 kg/m2, history of VTE, known thrombophilia, active cancer) and/or requiring ICU admission and/or with rapidly increasing D-dimer levels, taking into account renal function and bleeding risk. Anticoagulation at treatment doses cannot be currently recommended in absence of confirmed VTE or ECMO therapy (32). These recommendations were made prior to the publication of the multiplatform trials (48) (see below).
- Prior to the announcement of the early stopping of the three major clinical trials discussed above (REMAP-CAP, ACTIV-4a, ATTACC), Algerian Society of Thrombosis and Hemobiology recommended a more aggressive approach to anticoagulation, suggesting that therapeutic doses of anticoagulation be used for obese patients with added risk factors for thrombosis or those with artificial ventilation. They also recommend extended thromboprophylaxis in patients with added risk factors for thrombosis e.g. prolonged immobilization, age > 70 years, history of VTE, comorbidities such as active cancer, and D-dimer > 2x the normal upper reference range (33).
- BSTH and the ABHH suggest standard doses of thromboprophylaxis adjusted for body weight and renal function due to the lack of evidence of benefit of higher intensity thromboprophylaxis. They also suggest post-discharge thromboprophylaxis for COVID-19 patients who are high risk (17). These society guidance statements did not yet incorporate the most recent RCT data as described above.

Extended Duration VTE prophylaxis

- The practice of extending thromboprophylaxis with LMWH or DOAC for up to 30-days post-discharge in acutely ill medical patients is based on studies conducted prior to the COVID-19 pandemic (34-36). These studies demonstrated the efficacy of extended duration prophylaxis in the reduction of VTE events, but was associated with increased bleeding events. However, no studies have reported the outcomes of this strategy in COVID-19 patients.
- Post-discharge VTE data from an ongoing quality improvement program based out of King's College in the UK found that the rate of symptomatic post-discharge VTE following hospitalization with COVID-19 is low (4.8 per 1000 discharges), and not significantly higher than post-discharge VTE following non-COVID-19 hospitalizations (3.1 per 1000 discharges) (37).
- The current CHEST guidelines tentatively recommend against extended thromboprophylaxis at the time of publication pending emerging data on post-discharge VTE risk (26). However, others have suggested that this be considered on an individual basis based on VTE risk factors (32, 38). Of note, no randomized controlled trials have been reported to support either practice.

Synthesis of the Information Relating to Question 3

- Many societies made recommendations as described above prior to the availability of robust randomized controlled trial data such as the multiplatform trials (48) and HEP-COVID (51). At the time of writing of this review, many had not yet updated their recommendations.
- Rates of symptomatic VTE post-discharge in patients who were hospitalized for COVID-19 are low. Given this, and the lack of RCTs, there is no evidence to suggest benefit in universal extended duration thromboprophylaxis. Although there is ongoing clinical controversy internationally, North American societies recommend against extended duration thromboprophylaxis based on the paucity of evidence and lack of signal for net benefit.

Research Question 4 – Prevention of organ support and ICU-level care

Does therapeutic anticoagulation confer additional clinical benefit over prophylactic anticoagulation in specific groups of hospitalized COVID-19 patients?

- The multiplatform trials, (REMAP-CAP, ACTIV-4a, ATTACC), demonstrated increased probability of survival until hospital discharge without the need for ICU-level organ support at 21 days as compared to standard thromboprophylaxis in patients with moderate severity COVID-19 pneumonia (48).
- The trial did not increase the probability of survival to hospital discharge or number of days free of cardiovascular or respiratory organ support in critically ill patients. In fact, there was a 95% probability of being inferior to, and an 89% probability that therapeutic dose anticoagulation led to lower survival to hospital discharge than with usual care pharmacological thromboprophylaxis and a more significant increase in bleeding complications (53).

Evolving Evidence

There are numerous ongoing trials investigating the use of higher intensity pharmacological thromboprophylaxis and utility of extended duration post-discharge thromboprophylaxis. Table 1 and Table 2 provide examples of such trials respectively, although they are not all-encompassing.

Table 1. Ongoing clinical trials investigating higher intensity thromboprophylaxis

Trial name	Intervention	ClinicalTrials.gov identifier	Estimated Date of completion
X-Covid 19	Intermediate vs. prophylactic doses of enoxaparin	NCT04366960	November 2020
COVID-PREVENT	Rivaroxaban 20mg vs prophylactic doses of LMWH	NCT04416048	May 30, 2021
Covid-19 associated coagulopathy	Intermediate vs prophylactic doses of enoxaparin	NCT04360824	April 16, 2021
COVID-DOSE	Weight-based intermediate vs prophylactic doses of LMWH	NCT04373707	November 2021
INHIXACOV19	Weight-based intermediate vs prophylactic doses of enoxaparin	NCT04427098	October 30, 2020

Table 2. Ongoing clinical trials investigating extended duration thromboprophylaxis

Trial name	Intervention	ClinicalTrials.gov identifier	Estimated Date of completion
MICHELLE	Rivaroxaban 10mg for 35 days post-discharge	NCT04662684	June 30, 2021
COVID-19 Thrombosis Prevention Trials: Post-hospital Thromboprophylaxis	Apixaban 2.5mg for 30 days post-discharge	NCT04650087	September 2021
Effect of the Use of Anticoagulant Therapy During Hospitalization and Discharge in Patients with COVID-19 Infection	Therapeutic vs prophylactic enoxaparin during hospitalization, followed by Rivaroxaban 10mg post-discharge	NCT04508439	December 30, 2020

Table 3. Comparison of low molecular weight and unfractionated heparin dosing (assuming normal renal function and average body weight)

Drug name	Prophylactic dose	Intermediate dose	Therapeutic dose
Enoxaparin	40mg SC daily	40mg SC twice daily	1mg/kg SC q12h
Fondaparinux	2.5mg SC daily	n/a	7.5mg SC daily
Tinzaparin	4500 units SC daily or 75 units/kg weight >80 kg	n/a	175 units/kg SC daily
Unfractionated Heparin	5000 units SC twice or three times daily	7500 units SC q8h	Weight-based IV infusion protocol

Table 4. Comparison of available guideline recommendations

Organization	Routine VTE screening	Universal intensification of pharmacological thromboprophylaxis	Extended duration thromboprophylaxis
CHEST (24)	Against	Against	Against
ASH (39)	n/a	Against	No specific recommendation
ISTH (40)	Against	Against*	Should be considered for patients with high VTE risk
CDC (41)	No specific recommendation	Against	Against
ACC (30)	Against	Against*	n/a
SISET (42)	For	Can be considered	For

*minority of the panel/respondents considered intensification reasonable

Appendix
List of Abbreviations

VTE – venous thromboembolism
DVT – deep vein thrombosis
PE – pulmonary embolism
CT – Computed tomography
RCT – Randomized controlled trials
ASH – American Society of Hematology
ESC – European Society of Cardiology
CHEST – American College of Chest Physicians
SISET – Italian Society for Haemostasis and Thrombosis
BSTH – Brazilian Society of Thrombosis and Haemostasis
ABHH – Brazilian Association of Hematology, Hemotherapy, and Cellular Therapy
SATH – Algerian Society of Thrombosis and Hemobiology
ISTH – International Society of Thrombosis and Haemostasis
ACC – American College of Cardiology

Methods

Literature Search

A literature search was conducted by Rachel Zhao from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published from January 1, 2021 to Sept 24, 2021, and included: OVID MEDLINE, PubMed, TRIP Database Pro, CADTH, Canadian Medical Associations Clinical Guidelines, US CDC, CEBM Oxford COVID-19 Evidence Service, COVID-19 Primer, COVID-19 Evidence Reviews, European Centre for Disease Prevention and Control, Evidence Aid, National Collaborating Centre for Methods and Tools, UK NICE, and WHO COVID-19 Database.

Briefly, the search strategy involved combinations of keywords and subject headings including:

- Coronavirus or Coronavirus Infections or COVID-19 or COVID19 or COVID-2019 or COVID2019 or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARSCoV19 or SARS-Cov-19 or SARSCov-19 or SARSCoV2019 or SARS-Cov-2019 or SARSCov-2019 or severe acute respiratory syndrome coronavirus* or severe acute respiratory syndrome cov 2 or 2019 ncov or 2019ncov.
- Thromboembolism or venous thromboembolism or pulmonary embolism
- Limited to English language.
- Limited to randomized clinical trial, guideline, meta-analysis, practice guideline, review or systematic review

Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Table 1 below. 370 articles were identified by KRS with references and abstracts provided for further review. 240 articles were excluded from the review in accordance with the inclusion/exclusion criteria stated below.

Table 1. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
- All settings were included – in-patient and outpatient settings - Studies were limited to those published in 2020 to identify the most recent evidence in this rapidly evolving field - Due to novelty of this infection and the paucity of randomized controlled trials, reviews of all article types were included. - Only English language articles were included to facilitate the rapid review process - Studies were not excluded based on publication status, to identify the most up to date data. - All geographic locations were considered	- Article is not from a credible source - Article does not have a clear research question or issue - Presented data/evidence is not sufficient to address the research questions

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 2 below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the Cochrane Library, and the AGREE Trust (43-46).

Table 2. Narrative overview of the literature included in this review.

	Description
Volume	• 20 guidelines and position statements were included, 25 meta-analysis were included, 12 systematic reviews were included and 73 narrative reviews were included. 7 RCTs were added to this revision as well as 3 additional observational studies.
Quality	• Overall, recommendations identified in all article types were based on moderate-quality evidence due to of the new inclusion of several robust, large scale randomized clinical trials. • Recommendations for universal screening, intensified VTE prophylaxis and extended duration prophylaxis fail to take into consideration increased bleeding risk in this population and may result in an increase in major bleeding events. These recommendations are made in the absence of evidence of their clinical benefit.
Applicability	• Studies examining the prevalence of VTE in COVID-19 patients include a wide geographical range, many of which are generalizable to a single-payer, universal healthcare system such as Alberta.
Consistency	• Studies consistently demonstrate that patients with COVID-19 are at high risk of VTE, despite routine prophylaxis. • Guidelines differ greatly regarding their recommendations for universal screening, intensified VTE prophylaxis and extended duration prophylaxis, largely due to the absence of more robust evidence.

Search Strategy

A search for RCTs was conducted in OVID MEDLINE, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), and International Clinical Trials Registry Platform (ICTRP).

Ovid MEDLINE(R) ALL 1946 to October 06, 2021

#	Searches	Results
1	exp Coronavirus/ or Coronavirus Infections/ or coronaviru*.mp. or corona viru*.mp. or ncov*.mp. or n-cov*.mp. or novel cov*.mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-CoV-2.mp. or SARSCoV-2.mp. or SARSCoV2.mp. or SARSCoV19.mp. or SARS-Cov-19.mp. or SARSCov-19.mp. or SARSCoV2019.mp. or SARS-Cov-2019.mp. or SARSCov-2019.mp. or severe acute respiratory syndrome coronaviru*.mp. or severe acute respiratory syndrome cov 2.mp. or 2019 ncov.mp. or 2019ncov.mp.	202188
2	thromboembolism/ or venous thromboembolism/	37333
3	Pulmonary Embolism/	40759
4	(thromboembol* or thrombo embol* or venous thrombo* or vein thromb* or pulmonary embol* or lung embol* or pulmonary thromboembol* or lung thromboembol* or lung microemb* or pulmonary microemb*).kf,tw.	139724
5	or/2-4	159199
6	1 and 5	3012
7	((randomized controlled trial or controlled clinical trial).pt. or ((randomized or randomly or controlled) and (trial or trials)).ab.) not (exp animals/ not exp humans/)	891932
8	6 and 7	106
9	limit 8 to (english language and yr="2021 -Current")	57

57 results were retrieved. 24 were kept.

Cochrane Central Register of Controlled Trials (CENTRAL)

ID	Search
#1	MeSH descriptor: [COVID-19] explode all trees
#2	(coronaviru* OR "corona virus" OR ncov* OR n cov* OR COVID-19 OR COVID19 OR COVID-2019 OR COVID2019 OR SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019 OR "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*" OR "2019 ncov" OR 2019ncov OR Hcov*):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Thromboembolism] explode all trees
#5	MeSH descriptor: [Venous Thromboembolism] explode all trees
#6	MeSH descriptor: [Pulmonary Embolism] explode all trees
#7	(thromboembol* or thrombo embol* or venous thrombo* or vein thromb* or pulmonary embol* or lung embol* or pulmonary thromboembol* or lung thromboembol* or lung microemb* or pulmonary microemb*):ti,ab,kw
#8	#4 or #5 or #6 or #7
#9	#3 and #8

Custom Range: 01/01/2021 to 24/09/2021. 62 results were retrieved.

ClinicalTrials.gov

Thromboembolism or Venous Thromboembolism or Pulmonary Embolism | COVID-19

- All studies: 15
- Studies with results: 0 (none)

International Clinical Trials Registry Platform (ICTRP)

Thromboembolism or Venous Thromboembolism or Pulmonary Embolism

Restricted to COVID-19: 54 results

Further restricted to With results only: 0 (none)

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