Scientific Advisory Group

COVID-19 Scientific Advisory Group Rapid Evidence Brief

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

January 11, 2021

Alberta Health Services

Physical distancing works

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Lay Summary

BACKGROUND

- Patients who are hospitalized with COVID-19 are at high risk for abnormal blood clot formation (most commonly of the veins of the legs), called deep vein thrombosis, and lung damage caused by these clots travelling into circulation of the lungs (called pulmonary embolism). 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 COVID-19 complications is always changing and the research in this area has been very fast moving, leading to possible differences in practices across Alberta. As well, there have been different recommendations around which hospitalized COVID-19 patients should have blood tests (D-dimer testing) and/or ultrasounds or CT scans to look for these complications.
- This review summarizes the medical literature summaries of best practices in these areas (systematic reviews, meta-analyses, and guidelines) to provide guidance around best practices in VTE prophylaxis to our medical teams looking after hospitalized patients with COVID-19.

KEY MESSAGES

- Hospitalized patients with COVID-19 are at increased risk for VTE, especially those who are admitted to Intensive care and those with severe COVID-19 infection.
- Traditional risk factors for VTE also apply to patients with COVID-19, so risk for VTE should be assessed in the same way as is usually done.
- The blood D-dimer test is often elevated in COVID-19 patients even without VTE, therefore it is not particularly helpful on its own in assessing for VTE and additional clinical assessment, and in some cases ultrasound or CT are needed to establish the diagnosis in people with symptoms of VTE.
- 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.
- Research into VTE prophylaxis is ongoing and guidance may change in the future.

RECOMMENDATIONS

- COVID-19 patients in hospital should receive the usual preventative blood thinners recommended for hospitalized patients at VTE risk unless there are contraindications (usually once daily low-molecular weight heparin products such as tinzaparin).
- Further testing should be done if there are signs or symptoms suspicious for VTE complications (such as unexplained high heart rate, low blood pressure, one sided leg swelling, worsening shortness of breath or low oxygen status, etc.) rather than relying on elevation in D-dimer blood tests.

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- Higher than usual preventative doses of blood thinners (which have been suggested to prevent VTE in COVID-19 patients) are not recommended as new evidence suggests that this increases bleeding risk without adding much benefit. COVID-19 patients should receive standard dosing for the usual length of therapy. Studies are continuing in this area and recommendations may change in the future.

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Authorship and Committee Members

Name	Contribution
Jensen Lau, Pishoy Gouda	Writing, original draft preparation
Elizabeth MacKay	Primary scientific reviewer
Leslie Skeith, Micheal Guirguis	Secondary scientific reviewers
Braden Manns & Lynora Saxinger	Scientific Advisory Group chairs (oversight and leadership responsibility, some writing and editing)
John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Melissa Potestio, Jeremy Slobodan, James Talbot, Brandie Walker, Nathan Zelyas	Discussion, revision, and approval of document

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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 for 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?

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.
- 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

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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 usual dosages of pharmacological thromboprophylaxis with LMWH.
    - 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) (included in the Well's criteria) 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, however the clinical significance of very high 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 > 1.0 mg/l at admission or > 3 mg/l during hospitalization are more predictive of VTE.
- The presence of either a Wells score for PE ≥2 points or a D-dimer value ≥1.0 mg/l is the most sensitive for PE diagnosis (sensitivity 92.9%, specificity 46.9%); while a D-dimer value ≥3.0 mg/l combined with a Wells score for PE ≥2 has the greater specificity (sensitivity 57.1%, specificity 91.6%, while D-dimer value≥ 3 mg/l alone was less specific (sensitivity 71.4%, specificity 87.9%).

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 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.
- Randomized clinical trials of the use of intensified and/or extended pharmacological thromboprophylaxis in higher risk COVID-19 patients, are currently underway. Recently, three large randomized clinical trials (REMAP-CAP, ACTIVE-4, ATTACC) investigating the use of therapeutic anticoagulation dosing as prophylaxis in patients with COVID-19 have stopped recruitment of critically ill patients at the recommendation of the data safety and monitoring board due to an observed increased risk of harm with *therapeutic* dosing of anticoagulation.
- All guidelines identified in our review were published before the announcement that the above trials have stopped recruitment of critically ill patients.

Recommendations

Recommendation 1: All hospitalized COVID-19 patients should receive pharmacological thromboprophylaxis at standard daily prophylactic doses of LMWH, adjusted for weight and renal function, in the absence of contraindications. In Alberta, this would suggest the use of tinzaparin at 75 u/kg weight based dosing be used for the duration of the hospitalization. If pharmacologic thromboprophylaxis is contraindicated, then mechanical thromboprophylaxis with pneumatic compression stockings should be used until risk of bleeding subsides. (Patients with a history of HITT could receive fondaparinux for thromboprophylaxis).

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 DOAC's 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.

Recommendation 2: Diagnostic imaging for VTE with either ultrasound or CT-PE should only be undertaken only when there is a clinical suspicion and not based solely on D-dimer levels.
Additional testing to rule out PE should be considered in COVID-19 patients

- with unexplained hypoxia who have no significant chest X ray abnormalities, or worsening of CXR abnormalities
- with D-dimer result >=1 mg/l OR Well's criteria >=2
- D-dimer >3 mg/l and a Well's criteria greater >=2 has the highest sensitivity and specificity for a diagnosis of PE, and early diagnostic testing/empiric anticoagulation in the case of delay should be considered

Rationale: It is unknown whether there is clinical benefit to treating clinically silent VTE events identified on universal screening and there could be increased bleeding risk.
Clinical prediction risk tools, such as the Well's and modified Well's criteria for diagnosis of DVT or PE, with or without use of D-dimer, have been shown to improve diagnostic certainty and to reduce the burden of testing required.

Recommendation 3: Critically ill patients with COVID-19 and others with additional standard risk factors for VTE despite use of standard prophylaxis require a higher index of suspicion for VTE, and monitoring for features such as unexplained acute changes in oxygen requirements, new tachycardia or hypotension or asymmetrical limb swelling and pain is suggested to prompt further testing.

Rationale: Retrospective cohort studies consistently show increased risk of VTE in critically ill or more severe cases of COVID-19 and those with additional risk factors for VTE despite moderate use of standard prophylaxis in these populations.

Recommendation 4: Do not recommend extended post-discharge pharmacological thromboprophylaxis, based on current evidence.

Rationale: RCT's 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 COVID-19 patients are underway, which will inform future recommendations.

Recommendation 5: Do not recommend intensified thromboprophylaxis (intermediate or therapeutic dosing) based on current evidence. The use of therapeutic dosing of anticoagulants for VTE prophylaxis should not be done outside of Clinical Trials. Alberta clinicians could take part in the RAPID COVID COAG study if available at their site (REB#: REB20-0785 – PI: Dr. Suryanarayan).

Rationale: Three recent clinical trials examining the use of therapeutic dosage anticoagulation in severely ill patients with COVID-19 have been stopped early due to increased risk of bleeding. Formal results from these trials and ongoing clinical trials of subgroups with higher risk and lower risk of bleeding will inform future recommendations.

Practical Considerations

- Maintain a low threshold of 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 pharmacological thromboprophylaxis regimen that minimizes the number of interactions with COVID-19 patients. In Alberta, this would suggest standard prophylaxis dosing of tinzaparin 75u/kg (i.e. once daily injections) for the duration of the hospitalization.
- It may be reasonable to consider pharmacological thromboprophylaxis in acutely ill COVID-19 infected patients who are not hospitalized for other indications (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 and optimal 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.

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 prophylaxis in COVID-19 patients is based on low-quality observational evidence, expert opinion and data from other patient populations.

Limitations of this review

- This rapid review is based 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 heterogenous populations.

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).

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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 >1.5ug/ml had an 85% sensitivity, 88.5% specificity and negative

predictive value of 94.7% for detecting VTE (20). A D-dimer level >1ug/mL 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 > 1000 ng/ml or a Well's score > or = to 2 provided a sensitivity of 93% but specificity of 47% while a D-dimer of 3000 ng/ml and a Well's 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 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 this 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

- Many institutions have implemented intermediate-dose anticoagulation or full dose anticoagulation in patients at high-risk for developing VTE. This strategy has not been tested in large randomized clinical trials and is based solely on the observations that despite prophylactic anticoagulation, rates of VTE remain high, especially in the critical care setting (27, 28).
- Recently, three large randomized clinical trials (REMAP-CAP, ACTIVE-4, ATTACC) investigating the use of therapeutic anticoagulation in patients with COVID-19 have stopped recruitment of critically ill patients at the recommendation of the data safety and monitoring board due to an observed increased risk of harm with anticoagulation. Published results of these trials are pending.
- 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.
- 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).
- Prior to the announcement of the early stopping of the three major clinical trials discussed above (REMAP-CAP, ACTIVE-4, ATTACC), Algerian Society of Thrombosis and Hemobiology recommended a more aggressive with anticoagulation, suggesting that therapeutic doses of anticoagulation are used for obese patients with added risk factors for thrombosis or 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).
- There is a wide range of recommendations for the intensification of VTE prophylaxis and the use of extended duration prophylaxis. Either practice is based on the observation of an increased prevalence of VTE in this population and has not been examined in clinical trials.

Extended Duration VTE prophylaxis

- The practice of extending thromboprophylaxis with LMWH or DOAC up to 30-day post-discharge in acutely-ill medical patients is based on studies conducted prior to the COVID-19 pandemic (34-36), which demonstrated 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 CHEST guidelines tentatively recommends 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

- There is a lack of evidence of benefit for the use of intensified VTE prophylaxis in hospitalized COVID-19 patients. While patients with COVID-19 demonstrate higher thrombotic risk, they also demonstrate a higher bleeding profile, which are likely underestimated. Clinical trials comparing therapeutic to prophylactic dosing of anticoagulation in patients admitted in the ICU have recently been stopped early due to increased harm, with formal results pending.
- 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.

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**
RAPID COVID COAG	Therapeutic anticoagulation vs standard care	NCT04362085 REB#: REB20-0785 – PI: Dr. Suryanarayan	December 2021
COVID-HEP	Therapeutic anticoagulation vs standard care	NCT04345848	March 31, 2021
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	Therapeutic vs prophylactic enoxaparin during	NCT04508439	December 30, 2020

Therapy During Hospitalization and Discharge in Patients with COVID-19 Infection	hospitalization, followed by Rivaroxaban 10mg post-discharge		

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 for extremes of weight	n/a	175 units/kg SC daily
Unfractionated Heparin	5000 units SC twice 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

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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, 2020 to Dec 15, 2020, 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 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.
Quality	• Overall, recommendations identified in all article types were based on low-quality evidence due to the paucity of 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 any robust evidence.

Search Strategy

Sources searched: 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.

Dates searched: 1946 – Dec 15, 2020

Search Terms:

1. *Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)*

#	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.	103165
2	thromboembolism/ or venous thromboembolism/	35352
3	Pulmonary Embolism/	39260
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.	132781
5	or/2-4	151890
6	1 and 5	1433
7	limit 6 to (english language and yr="2020 -Current")	1378
8	limit 7 to (guideline or meta analysis or practice guideline or "review" or "systematic review")	274

2. **PubMed**

(((((("coronavirus"[MeSH Terms]) OR ("coronavirus infections"[MeSH Terms])) OR (coronaviru*[Title/Abstract] OR corona viru*[Title/Abstract] OR ncov*[Title/Abstract] OR n-cov*[Title/Abstract] OR novel cov*[Title/Abstract] OR COVID-19[Title/Abstract] OR COVID19[Title/Abstract] OR COVID-2019[Title/Abstract] OR COVID2019[Title/Abstract] OR SARS-CoV-2[Title/Abstract] OR SARSCoV-2[Title/Abstract] OR SARSCoV2[Title/Abstract] OR SARSCoV19[Title/Abstract] OR SARS-Cov-19[Title/Abstract] OR SARSCov-19[Title/Abstract] OR SARSCoV2019[Title/Abstract] OR SARS-Cov-2019[Title/Abstract] OR SARSCov-2019[Title/Abstract] OR severe acute respiratory syndrome coronaviru*[Title/Abstract] OR severe acute respiratory syndrome cov 2[Title/Abstract] OR 2019 ncov[Title/Abstract] OR 2019ncov[Title/Abstract])) AND ((((("Thromboembolism"[Mesh:NoExp]) OR "Venous Thromboembolism"[Mesh:NoExp]) OR "Pulmonary Embolism"[Mesh:NoExp]) OR (thromboembol*[Title/Abstract] OR thrombo embol*[Title/Abstract] OR venous thrombo*[Title/Abstract] OR vein thromb*[Title/Abstract] OR pulmonary embol*[Title/Abstract] OR lung embol*[Title/Abstract] OR pulmonary thromboembol*[Title/Abstract] OR lung thromboembol*[Title/Abstract] OR lung microemb*[Title/Abstract] OR pulmonary microemb*[Title/Abstract]))) AND (((((("guideline"[Publication Type]) OR ("meta analysis"[Publication Type])) OR ("practice guideline"[Publication Type])) OR ("review"[Publication Type])) OR ("systematic review"[Publication Type]))) AND (("english"[Language]) AND (("2020"[Date - Publication] : "3000"[Date - Publication])))

3. **TRIP Database Pro**

(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*) AND (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*) from:2020

Filter: Systematic Reviews

Filter: Guidelines

4. **WHO COVID-19 Database**

thromboembolism or "pulmonary embolism"

Type of study:
- Clinical Practice Guide
- Systematic review (remover)
- Evidence synthesis

Language
- English

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