Venous Thromboembolism (VTE) Prophylaxis for COVID-19

island health

Date Dec 9 – Version 4

PREPARED FOR:	Clinicians Involved in Caring for Patients with COVID-19
STANDARD TITLE:	Venous thromboembolism (VTE) prophylaxis for COVID-19

Summary of Recommendations

1. We suggest that all critically ill patients admitted to the ICU with COVID-19 receive intermediate-dose VTE prophylaxis, unless contraindicated. The choice of agent and dose should consider the patient's weight and renal function. We recommend the following for intermediate-dose VTE prophylaxis:

	Dose based on estimated glomerular filtration rate (eGFR)		
Weight (kg)	eGFR greater than or equal to 30mL/min	eGFR 20 to 29mL/min	eGFR less than 20mL/min
40-100	Enoxaparin 30mg SUBCUT q12h	Enoxaparin 40 mg SUBCUT q24h	Heparin 5000 units SUBCUT q8h OR Consider clinical pharmacy consult for consideration of non-formulary Tinzaparin
Greater than 100	Enoxaparin 40mg SUBCUT q12h	Enoxaparin 60 mg SUBCUT q24h	Heparin 7500 units SUBCUT q8h OR Consider clinical pharmacy consult for consideration of non-formulary Tinzaparin

2. We recommend standard VTE prophylaxis in ward patients admitted with COVID-19.

3. We recommend against extended pharmacologic thromboprophylaxis post discharge unless the thrombosis risk is considered to be very high (e.g. COVID-19 and post-surgical, or to be determined by prescriber) and the risk of bleeding is low (including low risk of mechanical fall).

4. Consider reassessing and holding thromboprophylaxis in patients with COVID-19 when the platelet count is $< 50 \times 10^9$.

5. We recommend continuing to explore involvement in clinical trials assessing different antithrombotic regimens in COVID-19 patients. Island Health is currently studying the feasibility of participating in the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) trial. If participation in national trials is not possible, we recommend locally led investigations that assess British Columbia-specific epidemiology, risk factors and anticoagulation-related outcomes, to arrive at the optimal VTE prophylaxis regimen for VIHA patients.

Situation

Studies describing the epidemiology, clinical outcomes, and treatment of SARS-CoV-19 (COVID-19) suggest that severe COVID-19 infection is likely a hypercoagulable state that leads to an increased risk of venous thromboembolism (VTE) and poorer prognosis. As a result, standard VTE prophylaxis regimens used in Canadian hospitals have been viewed to be potentially inadequate. There are several studies registered with ClinicalTrials.gov that are directly examining the relative efficacy and safety of enhanced VTE prophylaxis in patients with COVID-19, however, none have yet been completed. At present, alternative pharmacologic prophylaxis regimens have been proposed by various medical societies worldwide. This SBAR was developed in collaboration with VIHA clinical stakeholders, including Intensivists, Hospitalists, General Internists, Infectious Disease Specialists and Pharmacists to serve as an up-to-date summary of evidence and provide VIHA-specific guidance on VTE prophylaxis for hospitalized patients with COVID-19. The recommendations will be updated regularly with stakeholder feedback as more information becomes available.

Background

Currently, the standard VTE prophylaxis regimen for all in-patients at Island Health follows the 2017 Thrombosis Canada guideline and includes:

	Dose based on estimated glomerular filtration rate (eGFR)		
Weight (kg)	eGFR ≥ 30mL/min	eGFR 20 to 29mL/min	eGFR <20mL/min
40-100	Enoxaparin 40mg SUBCUT q24H	Enoxaparin 30mg SUBCUT q24H	Heparin 5000 units SUBCUT q12H

- For patients > 100kg: Enoxaparin 0.5mg/kg q24h (rounded to the nearest prefilled syringe 60mg, 80mg, 100mg, 120mg)
- For very high risk of VTE per Island Health recommendations: Enoxaparin 40mg SUBCUT q12H
- Other health authorities use: Enoxaparin 30 mg SUBCUT q12h as an option for specific patient populations such as orthopedic trauma and spinal cord injuries

In response to the pandemic, various medical societies, organizations and expert groups have made recommendations on VTE prophylaxis. While it is uniformly accepted that all hospitalized patients with COVID-19 should receive some form of pharmacologic prophylaxis, details pertaining to dosing vary.

Venous Thromboembolism (VTE) Prophylaxis for COVID-19

Below is Table 1, which is a summary of recent statements, guidance documents and reviews. At the present time, all are based on observational studies and expert opinion due to lack of randomized controlled trials.

Table 1: Summary of Societies and Guidance documents

Society/Guideline	Suggested VTE prophylaxis regimen	Platelet cut off for holding anticoagulation	Post-discharge prophylaxis	Date released/Updated
American Society of Hematology	- LMWH doses not specified - Dosage adjustments for obesity may be used per institutional guidance	- Hold if platelets < 20-30 x10^9/L or fibrinogen < 0.5g/L (no reference provided)	- Consider the individual patient's VTE risk factors at the time of discharge, including reduced mobility and bleeding risk, as well as feasibility	FAQ document Nov 30/Dec 1, 2020
The American College of Cardiology (ACC)	-Pharmacologic prophylaxis with LMWH or UF in all moderate to high risk patients unless otherwise contraindicated -Consider intermediate-dose or full anticoagulation in high-risk patients (consider this to be done within the context of a clinical trial)	- Not mentioned	- Consider post-hospital prophylaxis	June 12, 2020
American College of Chest Physicians (CHEST)	For critically ill: --pharmacologic prophylaxis with LMWH over UFH to limit staff exposure	-Not mentioned	-inpatient thromboprophylaxis over inpatient plus extended thromboprophylaxis	September 2020

	-standard dose over intermediate or full treatment dosing For non-critically ill: -pharmacologic prophylaxis with LMWH or fondaparinux over UFH to limit staff exposure -standard dose over intermediate or full treatment dosing			
Anticoagulation forum	<u>For critically ill patients:</u> - Enoxaparin 40mg SUBCUT BID, enoxaparin 0.5mg/kg SUBCUT BID, heparin 7,500 units SUBCUT TID or low intensity heparin infusion based on expert opinion <u>For non-critically ill patients:</u> -Standard dose VTE prophylaxis as per existing societal guidelines for medically ill and surgical hospitalized patients - For patients improving and transferring out of the ICU to the medical ward, de-escalate to standard VTE prophylaxis	- Hold if there is active bleeding or profound thrombocytopenia (threshold not indicated)	- Extended prophylaxis not necessary for all COVID 19 patients	Document published by Barnes et al May 21, 2020

Venous Thromboembolism (VTE) Prophylaxis for COVID-19

Canadian Agency for Drugs and Technologies in Health (CADTH)	- In hospitalized patients most Canadian and international guidance suggests using prophylactic dosing for VTE prophylaxis	- Not mentioned	- Most Canadian and international guidance does not suggest the routine use of extended prophylaxis unless considered high risk for VTE and low risk of bleed	Document to summarize the available limited evidence and not intended to provide recommendations Published report June 11, 2020
European Society of Cardiology	High risk of thromboembolism (labored breathing, RR greater than 24, decreased O2 saturations less than 90%, elevated CRP, D-dimer, and fibrinogen levels): -If admitted to the ICU then heparin IV infusion - If not admitted to the ICU enoxaparin 1mg/kg SUBCUT BID or heparin IV infusion Low risk: - If D-dimer greater than 3mcg/mL then enoxaparin 1mg/kg SUBCUT BID - If D-dimer 0.5 to 3mcg/mL then enoxaparin 40mg SUBCUT BID - If D-dimer less than 0.5mcg/mL then enoxaparin 40mg SUBCUT daily	- Not mentioned	- May require continued anticoagulation for a certain period following hospital discharge (duration not defined)	Correspondence in European Heart Journal by Attallah et al Apr 30th, 2020

Global COVID-19 Thrombosis Collaborative Group	- All hospitalized and critically ill patients with COVID-19 in the absence of contraindications should receive prophylactic anticoagulation - Optimal dosing remains unknown	- Not mentioned	- Extended pharmacological prophylaxis (up to 45 days) should be considered for patients at high risk of VTE who do not have a high risk of bleeding	Review published by Bikdeli et al May 30, 2020
National Institutes of Health (NIH)	- Hospitalized adults should receive VTE prophylaxis per the standard of care for other hospitalized adults - Insufficient evidence to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis outside the setting of a clinical trial	- Not mentioned	- Should not routinely be discharged on VTE prophylaxis - Using Food and Drug Administration-approved regimens extended prophylaxis can be considered in patients who are at low risk for bleeding and high risk for VTEs	Guidelines updated May 12, 2020
Public Health Agency of Canada	- Prophylactic LMWH or heparin SUBCUT BID is recommended. - Specific doses not stated	- Not mentioned	- Not mentioned	Guidance document August 17, 2020
Scientific and Standardization Committee (Comprised of multidisciplinary panel of	- ICU patients should receive routine thromboprophylaxis with prophylactic-dose UFH or LMWH. Intermediate	- Modification of dose should be considered for platelet counts of 50 x 10^9/L or 25 x 10^9/L	- Either LMWH or a DOAC can be used for extended duration thromboprophylaxis in selected populations at	Guidance document May 27, 2020

experts from the International Society on Thrombosis and Haemostasis ISTH)	dose LMWH can be considered for high risk patients. Obese patients can be considered for a 50% increase in the dose of thromboprophylaxis. Treatment dose should not be considered for primary prevention until the results of randomized controlled trials are available. Multi-modal thromboprophylaxis with mechanical methods can be considered. - Hospitalized patients should receive routine thromboprophylaxis with standard dose UFH or LMWH (preferred agent). Intermediate dose LMWH may also be considered.		high VTE risk and low bleed risk - If extended thromboprophylaxis is considered a duration of 14-30 days is recommended	
Thrombosis Canada	- Standard weight-adjusted VTE prophylaxis is recommended - Intermediate/intensified prophylaxis should be used ONLY if participating in a clinical trial	- Not mentioned	- Not routinely recommended - Can consider in select, high-risk medical inpatients on a case-by-case basis	Webinar and Q & A document Apr 23, 2020
World Health Organization (WHO)	- Pharmacological prophylaxis with LMWH	- Not mentioned	- Not mentioned	Interim Guidance May 2020

	according to local and international standards when not contraindicated - Doses not specified			

Assessment

The above-mentioned recommendations, although heterogeneous, are based on the same few publications that characterize the prevalence and potential prophylaxis of VTE in patients with COVID-19. The summary of this evidence is below in Table 1, and includes only studies that provide information on dosing regimens. As the BCCDC clinical reference group SBAR: Therapies for COVID-19 adopted the literature appraisal below, the content may appear similar.

VTE in critically ill patients admitted to ICU

Table 2: Observational studies of VTE prophylaxis regimens in ICU patients with COVID-19

Authors Date published	Population Location	VTE prophylaxis regimen	Results

Al-Samkari et al.
23/07/2020
	N= 400 Hospitalized COVID-19 patients (ICU=144 non-ICU=256)
	
	Boston, MA
		90% standard prophylaxis
		7% intermediate or full-dose anticoagulation
		3% mechanical prophylaxis only
			• ICU patients: 18.1% had a thrombotic event (7.6% venous, and 5.6% arterial)
			• Non-ICU patients: 4.7% had a thrombotic event (3.1% venous and 1.2% arterial)
			• Bleeding
			  • Overall bleeding: 4.8%
			  ○ ICU: 7.6%
			  ○ Non-ICU: 3.1%
			• Major bleeding: 2.3%

Bilaloglu et al. 20/07/2020	N= 3334 Hospitalized COVID-19 patients (ICU=829 non-ICU=2505) New York, US	All patients received prophylactic dosing anticoagulation	• ICU patients: 29.4% had a thrombotic event (13.6% venous, and 18.6% arterial) • Non-ICU patients: 11.5% had a thrombotic event (3.6% venous and 8.4% arterial) • A thrombotic event was associated with mortality adjusted HR 1.82; 95% CI 1.54-2.15; P<0.001)
Desborough et al. 27/05/2020	N=66 COVID-19 patients admitted to the ICU UK	Full anticoagulation with UFH IV infusion or prophylactic or renally dosed and/or weight based dalteparin SUBCUT once daily	• 11 (17%) were fully anticoagulated with UFH IV infusion • 55 (83%) received prophylactic dosing • 6 (9%) DVTs and 5 (8%) PEs – one patient had both a DVT and PE. All

			6 DVTs were associated with indwelling lines ● D-dimer levels on admission to the ICU were 69.1mg/L vs 2.1mg/L (median) for those who went on to have a VTE vs not p=0.005 ● Major bleeding occurred in 7 (10.6%) patients ● Patients that developed a VTE had a similar mortality rate to those who did not
Helms et al. 22/04/2020	N=150 COVID-19 patients with ARDS admitted to the ICU compared to N=233 non-COVID-19 patients with ARDS admitted to the ICU France	<u>COVID-19 with ARDS</u> 70% of patients received prophylactic dosing with LMWH at 4,000 units per day (equivalent to enoxaparin 40mg/day) or if contraindicated, unfractionated heparin at 5-8 units/kg/hr (equivalent to 8,000 units to 13,500 units per day for a 70kg patient) -30% of patients received full dose <u>Non-COVID-19 with ARDS</u> -80% of patients received prophylactic dosing as above vs 20% received full dose	● Thrombotic complications (mainly PE) was higher in those with COVID-19 vs non-COVID-19 patients (11.7% vs. 2.1%; p < 0.008)
Klok et al. 10/04/2020	N=184 COVID-19 patients admitted to the ICU Netherlands	Nadroparin 2,850 units SUBCUT daily up to 5,700 units SUBCUT BID based on weight x 7 days or more. Note: Nadroparin 4000 units is equivalent to enoxaparin 40mg.	● VTE incidence was 31% (95% CI 20-41%) after a 7-day follow-up - this result was not adjusted for the actual doses of nadroparin administered ● Age, prolonged PT and PTT were independent predictors of thrombotic complications ● Mortality was not reported, however it was reported that thrombotic complications were at higher risk of all-cause death (HR 5.4, 95% CI 6.1-27)
Lemos et al. 15/09/2020	N=20 COVID 19 patients admitted to the ICU	Therapeutic anticoagulation (for 4 to 14 days) vs standard prophylactic anticoagulation (enoxaparin 40mg if weight <	● Statistically significant increase in PaO2/FiO2 ratio in the therapeutic anticoagulation group. Not observed in the prophylactic group

		120kg and 40mg BID if weight > 120kg, or UFH 5000 units SUBCUT TID if weight < 120kg and 7500 units SUBCUT TID if weight > 120kg)	• Higher ratio of successful liberation from mechanical ventilation (HR 4 (CI 1.04-15.06)) and more ventilator free days (15 days vs 0 days) for the therapeutic anticoagulation group vs prophylactic group • No difference in all cause mortality • Small study
Llitjos et al. 22/04/2020	N=26 COVID-19 patients admitted to the ICU France	Exact regimens were not reported however all patients received anticoagulation with LMWH or heparin	• 31% of patients received prophylactic anticoagulation vs 69% received therapeutic anticoagulation • The cumulative rate of VTE in patients was 69% (N=18). VTE was significantly higher in patients treated with prophylactic anticoagulation vs full anticoagulation (100% vs 56% p=0.03).
Paranjpe et al. 05/05/2020	N=2733 with confirmed COVID-19 New York, USA	Treatment dose systemic anticoagulation (including oral, SUBCUT, or IV forms)	• 786 (28%) patients received therapeutic dose anticoagulation during their hospital course. • Anticoagulated patients were more likely to require mechanical ventilation (29.8% vs 8.1% p<0.001). • 395 (14.4%) of patients were intubated and critically ill, and of those patients, in-hospital mortality was 29.1% in those receiving therapeutic anticoagulation vs 62.7% for those patients not receiving therapeutic anticoagulation • Therapeutic anticoagulation was associated with a reduced risk of mortality HR 0.86 (95% CI 0.82-0.89) • Bleeding was reported in 1.9% of patients not treated with therapeutic anticoagulation vs 3% in patients treated with

			therapeutic anticoagulation (p=0.2) • Bleeding was more common among patients intubated 30/395 (7.5%) vs non-intubated patients 32/2378 (1.35%).
Poissy et al. 24/04/2020	N=107 COVID-19 patients admitted to the ICU compared to N=196 patients admitted to the ICU during the same time interval in 2019 France	Exact regimens were not reported however all patients received thromboprophylaxis with LMWH or heparin	• Despite a similar severity score on admission to the ICU, the frequency of PEs in the COVID group was 20.6% vs 6.1% in the non-COVID group admitted to the ICU in the same time interval in 2019 (absolute increased risk 14.4% 95% CI 6.1-22.8) • DVT in patients with COVID-19 4.7% vs 4.6% in non-COVID patients admitted to the ICU in the same time interval in 2019
Yin et al. 03/04/2020	N=449 COVID 19 patients admitted to the ICU compared to N=104 patients with non-COVID pneumonia admitted to the ICU) Wuhan, China	Enoxaparin 40-60mg SUBCUT Q24H or Heparin 10,000 to 15,000 units SUBCUT daily X 7 days (or more)	• Only 22% vs 21.1% received VTE prophylaxis • No difference in mortality for those that received VTE prophylaxis to those that did not in both groups (30.3% vs. 29.7%; 13.6% vs. 15.9%) • When D-dimers exceeded 6X the upper limit of normal, VTE prophylaxis lowered mortality in the COVID-19 group (32.8% vs 52.4% p=0.017) but not in the non-COVID group
Wijaya et al. 20/10/2020	Systematic review and meta-analysis Therapeutic-dose anticoagulation and its effects on mortality (ward and ICU patients) N=8 studies	Types and doses of therapeutic anticoagulation mostly inadequately described	• 2 retrospective cohort studies showed a significant reduction of mortality in mechanically-ventilated patients • 1 study showed a reduction in mortality in elderly patients • 5 studies showed no mortality benefit

ICU patients can have many risk factors for VTE. With the exception of the Yin, Helms and Poissy et al (2020), the results of the above-mentioned studies do not directly compare the rates of VTE in the ICU with COVID-19 to those in the ICU for other reasons. As such, it is difficult to infer whether the observed high risk of VTE is due to COVID-19 alone, or variables such as differing standards of care, variations in VTE screening practices, higher acuity of patients admitted to ICUs outside of Canada or lack of system capacity in a pandemic setting. To put these rates into a Canadian context, a large, multicentre trial of VTE prophylaxis in the critically ill, the PROTECT study (2011), is often cited as an indirect comparison. In this multicentre randomized trial, ICU patients received either dalteparin (5000 units SUBCUT daily plus placebo once daily) or unfractionated heparin (5000 units SUBCUT BID). While there was no difference between the two regimens, the rate of proximal leg VTE was 5-6% and PE was 1-2%. These rates give insight into the expected baseline prevalence of VTE in ICU patients on prophylaxis locally. This baseline rate appears lower compared to the rates currently published for critically ill patients with COVID-19. Based on the current literature, the prevalence of VTE in critically ill patients with COVID-19 has ranged widely from 7.7% (Goyal et al 2020) up to 79.4% (Nahum et al 2020). This variation likely reflects the variations in practice previously described, but does suggest an increase from the baseline prevalence.

There are currently five studies registered with ClinicalTrials.gov looking at different anticoagulation regimens in patients with COVID-19 in the ICU. See Appendix C Table 1 describing the ongoing clinical trials.

VTE in non-critically ill patients admitted to the general ward

Limited data on non-ICU patients with COVID-19 suggests that the incidence of VTE in non-ICU patients is lower than those who are admitted to ICU, although the incidence is likely elevated compared to other non-ICU hospitalized patients. As reviewed above, some expert guidelines and statements have made distinguishing recommendations based on severity of illness or care location (ICU vs. ward). The BCCDC Covid-19 Therapeutics Committee has downgraded the wording of their recommendations for increased enoxaparin dosing in ward patients to "consider" from "suggest" based on a lack of available evidence at this time. Table 3 lists the details of observational studies that reported VTE prophylaxis regimens and outcomes in non-critically ill patients with COVID-19. Some of the studies did not separate the analysis of ICU and non-ICU patients, making it challenging to interpret the results.

Table 3: Observational studies of VTE prophylaxis regimens in hospitalized patients with COVID-19

Authors Date published	Population Location	VTE prophylaxis regimen	Results

Lodigiani et al 20/04/2020	N=388 hospitalized patients with COVID-19 Milan, Italy	ICU patients: Prophylactic dosing with LMWH (weight adjusted) Non-ICU patients: Prophylactic, intermediate and full dose anticoagulation	• 84% (N=326) of patients were admitted to the ward and 16% (N=62) to the ICU • Cumulative rate of thromboembolic events: ICU patients 27.6% vs 6.6% in non-ICU patients • There was no association with the dose of thromboprophylaxis received and the rate of venous or arterial thromboembolism
Lynn et al 28/10/2020	N=402 hospitalized patients with COVID 19 (N=108 in ICU and N=294 in non-ICU) Washington, DC, USA	Therapeutic anticoagulation considered if D-dimer > 3 ug/mL otherwise standard prophylactic dosing anticoagulation used	• Increased mortality was associated with therapeutic AC (OR 3.42 95% CI 2.06-5.67) • Critically ill and intubated patients had similar survival curves regardless of anticoagulation dose • 9% of patients receiving therapeutic anticoagulation experienced clinically significant bleeding vs 3% for prophylactic anticoagulation
Middledorp et al 19/04/2020	N= 198 hospitalized patients with COVID-19 Netherlands	All patients received intensified VTE prophylaxis with weight-based nadroparin (2,850 or 5,700 IU BID), which is approximately equivalent to 30-60mg of enoxaparin BID	• 63% (N=124) were admitted to the ward and 39% (N=74) were treated in the ICU at some point during their hospital stay • Of the 21 symptomatic VTEs, 17 occurred in ICU patients and 4 in ward patients; ICU stay was independently associated with VTE risk, with a HR of 6.9 (95%CI 2.8-17) • The study characterized the high prevalence of VTE in critically ill patients despite intensified anticoagulation, and the much lower risk of VTE in ward-based patients. • Bleeding outcomes were not reported
Moll et al. 01/11/2020	N=210 hospitalized patients with COVID	Enoxaparin 40mg SQ daily or UFH 5000 units SUBCUT Q12H or Q8H	• Cumulative incidence of VTE in ICU=9.3%

	19 (N=102 in ICU, N=108 in non-ICU) Boston, MA		• No events occurred in ward patients
Nadkarni et al 20/08/2020	N = 4389 hospitalized patients with COVID-19 (both ICU and non-ICU) New York, NY	No anticoagulation vs prophylactic anticoagulation vs therapeutic anticoagulation	• At least 48 hours of some form of anticoagulation (prophylactic or therapeutic) was associated with a 53% reduction in mortality • There was no statistically significant difference in mortality between prophylactic versus therapeutic anticoagulation
Paolisso et al. 06/08/2020	N = 450 hospitalized patients with COVID-19 (both ICU and non-ICU) Bologna, Italy	Enoxaparin 40-60 mg SUBCUT daily vs enoxaparin 40-60 mg SUBCUT BID	• All-cause mortality was 13% lower in patients who received BID enoxaparin.
Santoliquido et al 06/07/2020	N=84 non-ICU hospitalized patients with COVID-19 Rome, Italy	Enoxaparin 40 mg SUBCUT daily or fondaparinux 2.5 mg SUBCUT daily	• 10 (11.9%) patients with DVTs • Majority were distal • Only 2 (2.4%) DVTs were symptomatic

There are currently five studies registered with ClinicalTrials.gov looking at different anticoagulation regimens in non- ICU hospitalized adult patients with COVID-19. See Appendix C Table 2 for information about these studies. Locally, VIHA will be participating in the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) collaborating with the University Health Network (UHN), Toronto, the University of Manitoba, and Hamilton Health Sciences Corporation. This will be a prospective, open-label randomized, multicentre trial to establish whether therapeutic anticoagulation improves outcomes for COVID-19 patients. Participants will be randomized to receive either therapeutic anticoagulation or prophylactic dosing anticoagulation according to local practices

Based on the lack of representation of non-severely ill patients treated outside of the ICU, no conclusions about optimal anticoagulation regimens for such patients can be made. What is clear from the literature is that hospitalized patients with COVID-19 should receive standard VTE prophylaxis at minimum, unless there is a strong contraindication. The role for higher dose prophylaxis or therapeutic anticoagulation in the absence of other indication remains unknown in these patients.

D-dimer levels and COVID-19

Elevated D-dimer levels may reflect acute VTE however, this test is non-specific and can be elevated in a variety of other conditions (e.g. malignancy, inflammatory conditions, and infections). Preliminary observational data suggests there may be a correlation with elevated D-dimer levels and increased incidence of VTE in critically ill patients (Cui et al 2020). Other data suggests high D-dimer levels (3-4 fold or greater than 1-2 mcg/mL) are associated with high mortality in patients with COVID-19 (Zhou 2020, Tang 2020, and Zang 2020). Currently, there is no evidence to support therapeutic anticoagulation based on D-dimer levels in COVID-19 patients in the absence of other compelling indications.

Recently, a Canadian trial led by St. Michael's Hospital has been designed to evaluate the optimal prophylactic regimen in non-ICU patients. The RAPID COVID COAG study is a pragmatic, randomized, controlled trial of therapeutic coagulation vs. standard of care of non-critically ill hospitalized patients with D-dimer elevated above 2 mg/L. The primary objective of the study is to evaluate whether full-dose, therapeutic anticoagulation in those with laboratory risk factors can prevent the development of critical illness, VTE and reduce mortality.

Pharmacologic Thromboprophylaxis post discharge

Due to limited published data, (see Table 4) it is unclear whether patients with COVID-19, compared to those hospitalized patients without COVID-19, are at continued risk for VTE at hospital discharge and how long this risk may last. In studies published to date, the risk of post-discharge VTE in COVID-19 patients appears to be similar to that of patients hospitalized for other acute medical illnesses.

Table 4: Observational studies of VTE in COVID-19 patients post-discharge

Authors Date published	Population Location	VTE prophylaxis regimen	Results
Patell et al 07/08/2020	N= 163 discharged COVID-19 patients (ICU admission=42) Boston, MA	None post-discharge	• 30-day post-discharge cumulative thrombosis (ATE and VTE) incidence: 2.5% (95% CI 0.8-7.6) • 30-day post-discharge cumulative incidence of VTE alone: 0.6% (95% CI 0.1-4.6) • 30-day post-discharge cumulative incidence of major bleed: 0.7% (95% CI 0.1-5.1) • 30-day post-discharge cumulative incidence of clinically relevant non-major bleed (CRNMB): 2.9% (95% CI 1.0-9.1) • 4/6 (67%) events of patients experiencing major bleed or

			CRNMB were related to mechanical falls post-discharge

Roberts et al 03/08/2020	N=1,877 COVID-19 patients discharged from hospital (ICU admission=208)
	N=18,159 medical patients discharged from hospital in 2019
	
	UK
		None post-discharge	• 42-day post-discharge VTE rate not statistically significantly higher:
			  • COVID-19 patients: 4.8 per 1000 discharges
			  • Non-COVID-19 patients: 3.1 per 1000 discharges

In patients without COVID-19, extended prophylaxis has been shown to have some benefit in some high-risk surgical patients however similar benefits have not been consistently seen in patients admitted for acute medical illness. Two recent meta-analyses (Bajaj et al 2019 and Zayed et al 2019) of 5 trials showed that extended duration prophylaxis (4-6 weeks) was associated with a reduction in rates of symptomatic VTE or VTE related deaths compared to standard of care: (0.8% vs 1.2% RR: 0.61, 95% CI 0.44-0.83). However, this was at the expense of increased risk of major or fatal bleeding 0.6% vs 0.3% RR: 2.04, 95% CI 1.42-2.91).

As outlined above, there are mixed recommendations in expert guidance statements and documents on this topic. At present, there is limited evidence to assess the benefits and risks of extending thromboprophylaxis post discharge and therefore we do not recommend routine use of extended prophylaxis after COVID-19 infection. In select high-risk VTE patients (e.g. COVID-19 and post-surgical, or to be determined by prescriber) with a low risk of bleeding (including a low risk of mechanical fall), extended prophylaxis may be considered on a case-by-case basis.

Currently, there are two studies registered with ClinicalTrials.gov looking at outcomes with extended prophylaxis post-discharge, both studying the impact of direct oral anticoagulants on thromboembolism prevention post-discharge. See Appendix C Table 3 for trial details.

Platelet cut-off for VTE prophylaxis in COVID-19

Hematological changes including thrombocytopenia are common in patients with COVID-19. Unfortunately, there is very limited evidence to guide platelet threshold for withholding pharmacologic thromboprophylaxis in COVID-19 patients. As discussed below under "Bleeding and COVID-19", Al-Samkari et al identified the following risk factors for bleeding complications during hospitalization for COVID-19: platelet count <150 x 10^9/L (OR 2.90, CI 1.05-7.99); D-dimer >2500 ng/mL at initial presentation (OR 3.56, CI 1.01-12.66). A sensitivity analysis assessing major bleeds specifically determined that only platelet count <150 x 10^9/L was predictive of major bleeds (OR 4.42, CI 1.09-17.91). Unfortunately, the sample size was small, and few patients were included in this analysis;

additionally it was not statistically appropriate to compare even lower thresholds (e.g. <100 x 10^9/L, <50 x 10^9/L, and <25 x 10^9/L).

As indicated above, the American Society of Hematology Frequently Asked Questions statement from December 1, 2020 recommended that in the absence of bleeding, prophylactic LMWH should only be held in patients with COVID-19 if platelet count is less than 20-30x10^9/L, or fibrinogen is less than 0.5 g/L, however no reference was provided.

The Padua risk score, a validated risk assessment model for VTE risk in all hospitalized medical patients, excluded patients from pharmacologic thromboprophylaxis if the platelet count was less than 100 x 10^9/L (Barbar et al 2010). Our local practice here at Island Health is to hold thromboprophylaxis when the platelet count is < 50 x 10^9/L. This threshold comes from the PROTECT study, assessing dalteparin versus UFH for thromboprophylaxis in critically ill patients, where pharmacologic thromboprophylaxis was held if the platelet count was less than 50 x 10^9/L (PROTECT Investigators 2011).

Bleeding and COVID-19

There is conflicting data on whether patients with COVID-19 are at increased risk for clinically significant bleeding. Earlier in the COVID-19 pandemic, published data suggested that clinically overt bleeding was uncommon in COVID-19 infection despite patients having abnormal coagulation parameters (Bikdeli et al 2020). In a recent systematic review and meta-analysis by Jimenez et al, that looked at the incidence of VTE and bleeding among hospitalized patients with COVID-19, the pooled incidence for bleeding was 7.8% (95% CI, 2.6-15.3) and 3.9% (95% CI 1.2-7.9) for major bleeding which is much higher than initially thought. The highest pooled incidence of bleeding was reported for patients receiving intermediate or full-dose anticoagulation. Al-Samkari et al identified the following risk factors for bleeding complications during hospitalization: platelet count <150 x 10^9/L (OR 2.90, CI 1.05-7.99), D-dimer >2500 ng/mL at initial presentation (OR 3.56, CI 1.01-12.66). A sensitivity analysis assessing major bleeds only determined that only platelet count <150 x 10^9/L was predictive of major bleeds (OR 4.42, CI 1.09-17.91).

If intermediate VTE prophylaxis dosing is considered, bleeding risk must also be considered. Several studies in the critically ill, trauma, and surgical population have compared enoxaparin 40mg SUBCUT daily to enoxaparin 30mg SUBCUT BID (Robinson et al 2013, Bush et al 2011, and Riha et al 2012). The bleeding rates were similar between the two dosing groups.

Special populations:

There is currently no evidence specifically aimed at addressing the optimal VTE prophylaxis regimens in special populations, such as those with obesity and renal dysfunction. While baseline characteristics of participants in several above-mentioned studies imply that those, for example, receiving continuous renal replacement therapy (CRRT) were included in the analyses, no conclusions have been derived that

directly address these populations. As such, currently available data on dosing in obesity and renal dysfunction in patients without COVID-19 is extrapolated to VTE prophylaxis in COVID-19 infection.

- **Adjustments to VTE Prophylaxis in Patients with Elevated BMI -** According to guidelines and current practices at Island Health, those with weight greater than 100 kg receive higher weight-based doses of enoxaparin or heparin.
- **Adjustments to VTE Prophylaxis in Patients with Renal Dysfunction** - As enoxaparin accumulates in renal failure even at prophylactic doses (Atiq et al 2015), guidelines and current Island Health recommendations are to use a reduced dose of enoxaparin for VTE prophylaxis if eGFR is 20-29mL/min and to use heparin if eGFR is less than 20 mL/min.

Recommendations

1. We suggest that all critically ill patients admitted to the ICU with COVID-19 receive intermediate-dose VTE prophylaxis, unless contraindicated, despite weak evidence. The choice of agent and dose should consider the patient's weight and renal function. We recommend the following for intermediate-dose VTE prophylaxis:

	Dose based on estimated glomerular filtration rate (eGFR)		
Weight (kg)	eGFR greater than or equal to 30mL/min	eGFR 20 to 29mL/min	eGFR less than 20mL/min
40-100	Enoxaparin 30mg SUBCUT q12h	Enoxaparin 40 mg SUBCUT q24h	Heparin 5000 units SUBCUT q8h OR Consider clinical pharmacy consult for consideration of non-formulary Tinzaparin
Greater than 100	Enoxaparin 40mg SUBCUT q12h	Enoxaparin 60 mg SUBCUT q24h	Heparin 7500 units SUBCUT q8h OR Consider clinical pharmacy consult for consideration of non-formulary Tinzaparin

2. We recommend standard VTE prophylaxis in ward patients admitted with COVID-19.
   Hospitalized patients should continue to receive:
   - Enoxaparin 40mg SUBCUT q24h if weight 40 to 100kg AND age less than 85 years AND eGFR greater than 30mL/min
   - Enoxaparin 30mg SUBCUT q24h if weight less than 40kg OR age greater than 85 or eGFR 20 to 29mL/min
   - Heparin 5000 units SUBCUT Q12H for eGFR less than 20mL/min
   - Enoxaparin 0.5mg/kg q24h (round to the nearest prefilled syringe 60mg, 80mg, 100mg, 120mg) for patients greater than 100kg

3. We recommend against extended pharmacologic thromboprophylaxis post discharge unless the thrombosis risk is considered to be very high (e.g. COVID-19 and post-surgical, or to be determined by prescriber) and the risk of bleeding is low (including low risk of mechanical fall).

4. Consider reassessing and holding thromboprophylaxis in patients with COVID-19 when the platelet count is $< 50 \times 10^9$.

5. We recommend continuing to explore involvement in clinical trials assessing different antithrombotic regimens in COVID-19 patients. Island Health is currently studying the feasibility of participating in the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) trial. If participation in national trials is not possible, we recommend locally led investigations that assess British Columbia-specific epidemiology, risk factors and anticoagulation-related outcomes, to arrive at the optimal VTE prophylaxis regimen for Island Health patients.

Appendix A: Stakeholder/Working Group

Chair: Name, Quality, Program; Site

Representative	Program	Site
Dr. John Antonsen	- Head of VIHA Division of Nephrology - Medical Director – VIHA renal services - Chair – BC Renal Hemodialysis Committee	RJH
Dr. Cameron Griffiths	- Hematologist Pacific Hematology	RJH
Dr. Daniel Ovakim	- ICU physician - Medical toxicologist BC Drug and Poison Information - Member of the BC CDC COVID therapeutics committee - Island Health COVID research co-lead	RJH/VGH
Dr. Eric Partlow	- Head of VIHA Division of Infectious Diseases	RJH/VGH
Dr. Adrian Yee	- Hematologist Pacific Hematology/BCCA	RJH/BCCA

Appendix B: References

1. Moores, L., Tritschler, T., Brosnahan, S., Carrier, M., Collen, J.Fk, ….. & Wells, P. (2020) Prevention, Diagnosis, and treatment of VTE in patients with coronavirus disease 2019;CHEST Guideline and expert panel report; 158:1143-63.
2. Barnes, G. D., Burnett, A., Allen, A., Blumenstein, M., Clark, N. P., Cuker, A., ... & Kaatz, S. (2020). Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *Journal of Thrombosis and Thrombolysis*, 1.
3. CADTH (2020). Venous Thromboembolism Prophylaxis in Patients Hospitalized with CCOVID-19. Ottawa. CADTH Horizon Scan.
4. Atallah B, Mallah SI, AlMahmeed W. Anticoagulation in COVID-19. *European Heart Journal – Cardiovascular Pharmacotherapy*. April 2020. doi:10.1093/ehjcvp/pvaa036
5. Bikdeli, B., Madhavan, M., Jimenez, D., Chuich, T., Dreyfuss, I., Driggin, E., Der Nigoghossian, C.,….Lip, G. (2020). Covid-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. *Journal of the American College of Cardiology;75:2950-73.*
6. Spyropoulos, A. C., Levy, J. H., Ageno, W., Connors, J. M., Hunt, B. J., Iba, T., ... & Douketis, J. D. (2020). Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19. *Journal of Thrombosis and Haemostasis*
7. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. *Blood*. 2020;136(4):489
8. Bilaloglu, S., Aphinyanaphongs, Y., Jones, S., Iturrate, E., Hochman, J., & Berger, J. S. (2020). Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA*.
9. Desborough MJR, Doyle AJ, Griffiths A, et al. Image-proven thromboembolism in patients with severe COVID-19 in a tertiarty critical care unit in the United Kingdom. *Thrombosis Research* 2020;193:1-4.
10. Helms, J., Tacquard, C., Severac, F., Leonard-Lorant, I., Ohana, M., Delanbranche, X., et al (2020); High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicentre prospective cohort study. Intensive Care Medicine (ICM). DOI: 10.1007/s00134-020-06062-x
11. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thrombosis Research* 2020;191:148-150.
12. Klok, F. A., Kruip, M. J. H. A., van der Meer, N. J. M., Arbous, M. S., Gommers, D. A. M. P. J., Kant, K. M., ... & Endeman, H. (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research*.
13. Lemos, A. C. B., do Espírito Santo, D. A., Salvetti, M. C., Gilio, R. N., Agra, L. B., Pazin-Filho, A., & Miranda, C. H. (2020). Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thrombosis Research*, *196*, 359-366.
14. Llitjos, J., Leclerc, M., Chochois, C., Monsaillier, J., Ramkers, M., Auvray, M., Merouani, K. (2020). High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *Journal of Thrombosis and Haemostasis*

15. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19. *Journal of the American College of Cardiology*. May 2020. doi:.
16. Poissy, J., Goutay, J., Caplan, M., Parmentier, E., Duburcq, T., Lassalle, F., ... & Susen, S. (2020). Pulmonary embolism in COVID-19 patients: Awareness of an increased prevalence. *Circulation*.
17. Yin, S., Huang, M., Li, D., & Tang, N. (2020). Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *Journal of Thrombosis and Thrombolysis*, 1.
18. Wijaya, I., Andhika, R., & Huang, I. (2020). The Use of Therapeutic-Dose Anticoagulation and Its Effect on Mortality in Patients With COVID-19: A Systematic Review. *Clinical and Applied Thrombosis/Hemostasis*, *26*, 1076029620960797.
19. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. (2011). Dalteparin versus unfractionated heparin in critically ill patients. *New England Journal of Medicine*, *364*(14), 1305-1314.
20. Jiménez, D., García-Sanchez, A., Rali, P., Muriel, A., Bikdeli, B., Ruiz-Artacho, P., ... & Monreal, M. (2020). Incidence of venous thromboembolism and bleeding among hospitalized patients with COVID-19: a systematic review and meta-analysis. *Chest*.
21. Goyal, P., Choi, J. J., Pinheiro, L. C., Schenck, E. J., Chen, R., Jabri, A., ... & Hoffman, K. L. (2020). Clinical Characteristics of Covid-19 in New York City. *New England Journal of Medicine*.
22. Nahum, J., Morichau-Beauchant, T., Daviaud, F., Echegut, P., Fichet, J., Maillet, J. M., & Thierry, S. (2020). Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Network Open*, *3*(5), e2010478-e2010478.
23. Lodigiani, C., Iapichino, G., Carenzo, L., Cecconi, M., Ferrazzi, P., Sebastian, T., ... & Sandri, M. T. (2020). Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thrombosis Research*.Lippi, G., & Plebani, M. (2020).
24. Lynn, L., Reyes, J. A., Hawkins, K., Panda, A., Linville, L., Aldhahri, W., ... & Teufel, K. (2020). The effect of anticoagulation on clinical outcomes in Novel Coronavirus (COVID-19) Pneumonia in a US Cohort. Thrombosis Research.
25. Middeldorp, S., Coppens, M., Haaps, T., Foppen, M., Vlaar, A., Muller, C., ... & van Es, N. (2020). Incidence of Venous Thromboembolism in Hospitalized Patient with COVID-19. *Preprints* 2020, 2020040345 (doi: 10.20944/preprints202004.0345.v1).
26. Moll, M., Zon, R.L., Sylvester PharmD, K.W., Chen, E.C., Cheng, V., ConnellMPH, N.T., Fredenburgh, L.E., Baron, R.M., Cho MPH, M.H., Woolley, A.E., and Connors, J.M. (2020). VTE in ICU patients with COVID-19. CHEST https://doi.org/10.1016/j.chest.2020.07.031 .
27. Nadkarni, G. N., Lala, A., Bagiella, E., Chang, H. L., Moreno, P., Pujadas, E., ... & Cordon-Cardo, C. (2020). Anticoagulation, mortality, bleeding and pathology among patients hospitalized with COVID-19: a single health system study. *Journal of the American College of Cardiology*.
28. Paolisso, Pasquale, Luca Bergamaschi, Emanuela Concetta D'Angelo, Francesco Donati, Maddalena Giannella, Sara Tedeschi, Renato Pascale et al. "Preliminary experience with low molecular weight heparin strategy in COVID-19 patients." *Frontiers in Pharmacology* 11 (2020): 1124.

29. Santoliquido A, Porfidia A, Nesci A, et al. Incidence of Deep Vein Thrombosis among non-ICU Patients Hospitalized for COVID-19 Despite Pharmacological Thromboprophylaxis. *J Thrombosis Haemostasis* 2020; https://doi.org/10.1111/jth.14992
30. Cui, S., Chen, S., Li, X., Liu, S., & Wang, F. (2020). Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*.
31. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Guan, L. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*.
32. Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*.
33. Zang, L., Yan, X., Fan, Q., Liu, H., Liu, X., Liu, Z., Zhang, Z. (2020), D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *Journal of Thrombosis and Haemostasis*.
34. Bajaj, N. S., Vaduganathan, M., Qamar, A., Gupta, K., Gupta, A., Golwala, H., ... & Mehra, M. R. (2019). Extended prophylaxis for venous thromboembolism after hospitalization for medical illness: a trial sequential and cumulative meta-analysis. *PLoS medicine*, *16*(4), e1002797.
35. Zayed, Y., Kheiri, B., Barbarawi, M., Banifadel, M., Abdalla, A., Chahine, A., ... & Bachuwa, G. (2020). Extended duration of thromboprophylaxis for medically ill patients: a systematic review and meta-analysis of randomised controlled trials. *Internal Medicine Journal*, *50*(2), 192-199.
36. Patell R, Bogue T, Koshy AG, et al. Post-discharge thrombosis and hemorrhage in patients with COVID-19. *Blood* 2020; https://doi.org/10.1182/blood.2020007938
37. Roberts LN, Whyte MB, Georgiou L, et al. Post-discharge venous thromboembolism following hospital admission with COVID-19. *Blood* 2020; https://doi.org/10.1182/blood.2020008086
38. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemostasis* 2010; 8(11): 2450-2457
39. Robinson, S., Zincuk, A., Larsen, U. L., Ekstrøm, C., Nybo, M., Rasmussen, B., & Toft, P. (2013). A comparative study of varying doses of enoxaparin for thromboprophylaxis in critically ill patients: a double-blinded, randomised controlled trial. *Critical Care*, *17*(2), R75.
40. Bush, S., LeClaire, A., Hampp, C., & Lottenberg, L. (2011). Review of a large clinical series: once- versus twice-daily enoxaparin for venous thromboembolism prophylaxis in high-risk trauma patients. *Journal of intensive care medicine*, *26*(2), 111-115.
41. Riha, G. M., Van, P. Y., Differding, J. A., Schreiber, M. A., & Oregon Health & Science University Trauma Research Group. (2012). Incidence of deep vein thrombosis is increased with 30 mg twice daily dosing of enoxaparin compared with 40 mg daily. *The American journal of surgery*, *203*(5), 598-602.
42. Atiq, F., van den Bemt, P. M., Leebeek, F. W., van Gelder, T., & Versmissen, J. (2015). A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency. *European journal of clinical pharmacology*, 71(8), 921-929.

Appendix C: Trials registered with ClinicalTrials.gov evaluating pharmacologic thromboprophylaxis for VTE prevention in patients with COVID-19

Table 1: In ICU patients

ClinicalTrials.gov Identifier	Title	Study Design	Intervention	Status as of Dec 9, 2020
NCT 04406389	Anticoagulation in Critically Ill Patients with COVID-19 (IMPACT)	Single centre Randomized Open-Label N=186 NY, USA	Intermediate dose Enoxaparin 0.5mg/kg SQ Q12H or 0.5mg/kg SQ Q24H if CrCl <30mL/min UFH 7,500 units SQ Q8H or Fondaparinux 2.5mg SQ daily vs Therapeutic dose Enoxaparin or UFH or Fondaparinux or Argatroban	Start date: June 2020 Estimated completion: June 2021
NCT 04486508	Intermediate-dose vs Standard Prophylactic anticoagulation and statin vs placebo in ICU patients with COVID-19 (INSPIRATION)	Multicentre Randomized Open-label N=600 Iran, USA	Intermediate dose with enoxaparin or UFH and atorvastatin 20mg daily or placebo vs Standard prophylactic dose With enoxaparin or UFH and atorvastatin 20mg daily or placebo	Start date: July 2020 Estimated completion: Dec 2020
NCT 04367831	Intermediate or Prophylactic-dose anticoagulation for venous or arterial thromboembolism in severe COVID-19 (IMPROVE)	Single centre randomized, parallel N=100 NY, USA	Enoxaparin 1mg/kg SUBCUT once daily OR UFH at 10 units/kg goal of Anti Xa 01 to 0.3 U/mL vs Enoxaparin 40mg SUBCUT once daily or UFH heparin 5000 units SUBCUT Q8H	State date: May 2, 2020 Estimated completion: Apr 2021
NCT 04344756	Anticoagulation with COVID-19 Infection, Nested in the Corimmuno-19 Cohort (Corimmuno-coag)	Multi-centre, randomized controlled trial, open-label France	Tinzaparin 175 units/kg SUBCUT once daily vs Standard prophylactic dose anticoagulation	Start date: Apr 20, 2020 Estimated completion: Sept 30, 2020

NCT 04345848	Preventing COVID-19 Complications with Low and High dose anticoagulation (COVID_HEP)	Single centre Randomized Open-Label N=200 Switzerland	Therapeutic anticoagulation with enoxaparin or UFH vs Standard prophylactic dose with enoxaparin or UFH	Start date: Apr 2020 Estimated completion: Nov 2020

Table 2: In Hospitalized patients

ClinicalTrials.gov Identifier	Title	Study Design	Intervention	Status as of Dec 9, 2020
NCT 04362085	Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation vs Standard Care	Multicentre RCT Open-label N=462 Canada	Therapeutic anticoagulation with LMWH or UFH (nomogram) until discharge, 28 days or death vs LMWH, UFH or fondaparinux at prophylactic doses for acutely ill hospitalized medical patients	Start date: May 2020 Estimated completion: Dec 2020
NCT 04366960	Comparison of Two doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 patients	Open-label, multi-centre prospective randomized trial N=2712 Milan, Italy	Enoxaparin 40mg SUBCUT once daily vs Enoxaparin 40mg SUBCUT BID	Start date: May 14, 2020 Estimated completion: Nov 2020
NCT 04505774	Anti-thrombotics for Adults Hospitalized with COVID-19 (ACTIV-4)	Open-label, randomized, multi-centre NY, USA	Therapeutic LMWH or UFH vs Prophylactic LMWH or UFH	Start date: Sept 4, 2020 Estimated completion: Dec 2021
NCT 04394377	Full anticoagulation vs Prophylaxis in COVID-19: Coalizao Action Trial (ACTION)	Randomized trial, Multi-centre Parallel N=600 Brazil	Rivaroxaban 20mg daily OR Enoxaparin 1mg SUBCUT Q12H vs Standard prophylaxis dosing	Start date: June 21, 2020 Estimated completion : Dec 2020

NCT 04512079	FREEDOM COVID-19 Anticoagulation Strategy (FREEDOM COVID)	Prospective, multi-centre, open-label, randomized controlled trial	Enoxaparin 40mg SUBCUT once daily vs Enoxaparin 1mg/kg SUBCUT Q12H vs Apixaban 5mg PO Q12H	Start date: Sept 8, 2020 Estimated completion: June 2021

Table 3: Extended thromboprophylaxis post discharge

ClinicalTrials.gov Identifier	Title	Study Design	Intervention	Status as of Dec 9, 2020
NCT 04416048	Effect of Anticoagulation Therapy on Clinical Outcomes in COVID-19 (COVID-PREVENT)	Multicentre Prospective Randomized Open-label N=400 Germany	Rivaroxaban 20mg (adjusted for renal function) x 7 days (or while in hospital) then 10mg daily x 28 days when discharged vs Standard of care prophylactic LMWH or UFH	Not yet recruiting Last updated post: July 16, 2020
NCT04650087	COVID-19 Thrombosis Prevention Trials: Post-hospital Thromboprophylaxis	Multicenter, adaptive, randomized platform trial N=5320 USA	Apixaban 2.5mg BID on discharge x 30 days vs Placebo BID on discharge x 30 days	Not yet recruiting Last updated post: December 2, 2020

	Venous Thromboembolism (VTE) Prophylaxis for COVID-19	

PREPARED BY:	APPROVED BY:	DATE
Anna Maruyama, PharmD (ICU) Celia Culley, PharmD (CCU/ CVU) Dr. Shavaun MacDonald, MD FRCPC (Emerg/ICU) Erica Otto, PharmD (ICU) Jolanta Piszczek, PharmD (AMS)		
	RECEIVED BY:	
	Name and Title	
This document has served as a source of information to the BCCDC thrombosis subcommittee as one of the authors of this document also sits on the BCCDC thrombosis subcommittee.		

Document History

Version	Date	Created/amended by	Approved by	For