The effect of heparin type & symptom duration on noncritically ill patients hospitalized for COVID-19:

secondary analyses of an international multiplatform RCT

by

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Thesis Abstract

In patients with COVID-19, hospitalization is associated with progression to the need for ICU-level organ support and mortality. It is important to have effective treatments to slow or halt progression and to identify patients at high risk of progressing. Therapeutic-dose heparin reduces progression to organ support and mortality in noncritically ill patients hospitalized for COVID-19, however, the differential treatment effects for various heparin types are unknown. Symptom duration prior to hospitalization may impact disease progression and treatment effects of therapeutic-dose heparin.

This thesis evaluated 3 objectives: 1) differential treatment effects of therapeutic-dose heparin by heparin type, 2) effects of symptom duration on disease progression, and 3) effects of symptom duration on heparin treatment.

We analyzed heparin type in noncritically ill patients hospitalized for COVID-19 by performing a secondary analysis of patients enrolled in the ATTACC and ACTIV-4a randomized controlled trials. Analyses of symptom duration only included patients from ATTACC. Patients were enrolled between May 2020 and January 2021 in Brazil, Canada, Mexico, Spain, and the US. Patients were randomized to either usual care venous thromboprophylaxis or therapeutic-dose heparin. Treatment effects were modeled using proportional odds logistic regression within a Bayesian framework. The primary ordinal outcome consisted of 1) survival without organ support, 2) survival with organ support, and 3) death.

Analysis of heparin type comprised 832 patients assigned to usual care venous thromboprophylaxis and 987 to therapeutic-dose heparin (total n=1819), of whom 90% were administered enoxaparin (n=887). Therapeutic-dose enoxaparin likely reduced progression to organ support and mortality compared to usual care venous thromboprophylaxis (adjusted odds ratio [OR] 1.19 95% credible interval [CrI] 0.94-1.52, posterior probability [Pr] 92.5%). Analysis of non-enoxaparin heparins was limited by small sample sizes.

Analyses of symptom duration consisted of 499 patients assigned to usual-care venous thromboprophylaxis and 638 assigned therapeutic-dose heparin (total n=1137). Shorter symptom duration prior to admission was associated with increased progression to organ support and mortality (adjusted OR for 1 day less of symptoms 1.08, 95% CrI 1.04-1.13, Pr >99.9%) but likely did not modify treatment effects of therapeutic-dose heparin (Pr 27.2%).

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Sylvain	Lother	1		1	1		
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1. Background

1.1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the recent global pandemic of coronavirus disease (COVID-19), has resulted in more than 775 million infections and >7 million deaths worldwide [1]. More than 54,000 of these deaths have occurred in Canada[1]. COVID-19 has been associated with respiratory, thrombotic, and inflammatory complications which, in some patients, could result in disease progression, respiratory failure, and death[2–5].

Several pharmacologic treatments improve clinical outcomes in patients hospitalized for COVID-19 such as dexamethasone, remdesivir, tocilizumab, and therapeutic-dose heparin[6–9]. Heparin is an anticoagulant with anti-inflammatory and antiviral properties that is commonly used to prevent and treat blood clots. Compared to usual care venous thromboprophylaxis, therapeutic-dose heparin improves outcomes in noncritically ill patients hospitalized for COVID-19[10–12]. It is unknown whether a differential treatment effect exists among the various types of heparins used or if a therapeutic-dose of any type of heparin confers similar treatment benefits.

Patients hospitalized for COVID-19 who progress to require respiratory or cardiovascular organ support are more likely to experience poor clinical outcomes[5]. Predicting disease progression, however, is challenging and only a limited set of variables are known to be informative. Identification of patient or laboratory markers of disease progression has the potential to target clinical treatment decisions based on a patient's individual risk.

1.2 COVID-19, Coagulopathy, & Disease Progression

1.2.1 Thromboembolism & COVID-19

Patients hospitalized with COVID-19 are at increased risk of thrombosis, including venous and arterial events[2]. Venous thromboembolic events (VTE), which consist of deep vein thromboses (DVT) and pulmonary embolisms (PE), are the most common blood clots observed in COVID-19 and have been reported to occur in 2-41% of hospitalized patients in observational studies[3,13–17]. Arterial thromboembolic events, consisting of stroke and myocardial infarction (MI), occurred at lower rates (1-5%)[14,16,18]. Thrombotic estimates have varied widely and often depended on the availability of diagnostic tests[19].

While macrothrombi (i.e., large-vessel clots including VTE and arterial thromboembolic events) are commonly observed in COVID-19, microthrombi (i.e., small-vessel clots) also form in organ vasculature resulting in organ dysfunction and failure. Microthrombi are purported contributors to disease progression, morbidity, and mortality[20,21].

Infection with SARS-CoV-2 can lead to increased inflammation which further contributes to thrombosis, a process referred to in the literature as *thromboinflammation*[22,23]. Activation of the innate immune system combined with endothelial dysfunction contributes to the prothrombotic state seen in COVID-19, a process increasingly referred to as *immunothrombosis*[22]. These two concepts have broad definitions with considerable mechanistic overlap, and both contribute to sepsis, the body's overwhelming, and often life-threatening reaction to an infection.

Thromboinflammation

The SARS-CoV-2 surface spike protein facilitates attachment to human endothelial cells via the angiotensin-converting enzyme 2 (ACE2) receptor[24]. This binding induces a proinflammatory state associated not only with increased inflammatory cytokines and other markers of inflammation, but also upregulation of coagulation through platelet activation, activation of the coagulation cascade, and impaired fibrinolysis[22,23].

In COVID-19, respiratory failure is in large part mediated by pulmonary microthrombosis and inflammation that comprise lung capillary beds and the alveoli. This results in impairment of gas exchange causing hypoxia and, in some patients, respiratory failure. The pathophysiologic mechanisms promoting thromboinflammation are complex and poorly understood but appear to seminally involve downstream consequences of monocyte activation and the production of transcription factors called hypoxia induced factors (HIF) and damage associated molecular patterns (DAMP) which both elicit strong inflammatory responses[22].

Immunothrombosis

In COVID-19, monocytes and neutrophils are attracted to sites of infection through cytokine signaling[22]. In response to infection, activated monocytes express tissue factor on their surface. Tissue factor in turn promotes thrombosis via platelet activation and in vivo coagulation activation via the extrinsic pathway.

Neutrophils also have a unique procoagulant defense mechanism whereby they ensnare pathogens within an extracellular neutrophil protein-chromatin-histone complex called neutrophil extracellular traps (NETs). Reactive oxygen species generated by neutrophil NADPH oxidase have been shown to mediate NET release by several stimuli including numerous pathogenic bacteria[25]. In the process of trapping and killing pathogens, NETs also promote thrombosis through platelet and coagulation cascade activation. NETs have been recognized as important constituents of macro- and microthrombosis in sepsis and in COVID-19[22,26,27].

The complement system likewise contributes to increased thrombosis in COVID-19. The complement system is comprised of plasma proteins that result in direct killing of pathogens via formation of membrane attack complexes (MAC) and aid in antibody opsonization of infected cells[22,28].

1.2.2 Disease Progression in SARS-CoV-2 infection

Progression of COVID-19 is, in large part, a consequence of thrombosis and inflammation[16]. Respiratory symptoms are the result of pulmonary inflammation. Once hospitalized for COVID-19, patients often require supplementary respiratory support[29]. A proportion of hospitalized noncritically ill patients may worsen to become critically ill and require respiratory and/or cardiovascular support within an intensive care unit (ICU). Once a patient has progressed to ICU-level organ support, their risk of mortality is higher, as is the risk of long-term physical, mental, and cognitive sequelae[30].

1.2.3 Markers of Disease Progression

Biomarkers that predict disease progression have both prognostic value and can help clinicians select or modify treatments to optimize clinical outcomes. In COVID-19, D-dimer is a biomarker that can identify subpopulations of patients at risk of disease progression and thrombotic events[31–34]. D-dimer is formed when crosslinked fibrin is broken down and is a marker of both thrombosis and inflammation.

Baseline patient factors also appear to have prognostic value in COVID-19. Characteristics such as increasing age, male sex, the presence of diabetes, hypertension, chronic kidney disease (CKD), or obesity are all individually associated with increased risk of disease progression and need for ICU-level organ support in hospitalized patients[35–37]. Age and male sex are also significant univariate predictors of mortality in COVID-19[36]. It is likely that other unexplored descriptive characteristics have prognostic value and that a combination of readily available patient factors and biomarkers could meaningfully predict the risk of disease progression in hospitalized patients.

1.3 Heparin

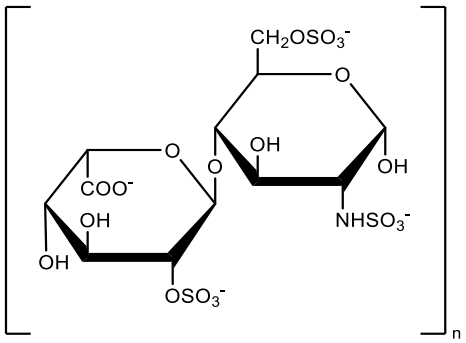
1.3.1 Properties of Heparins

Heparins are highly sulfated glycosaminoglycans of varying length with repeating subunits of sulfonated d-glucosamine, d-glucuronic, and l-iduronic acid (Figure 1.1)[38,39]. In therapeutic-doses, heparins are used to treat blood clots. In lower prophylactic-doses heparins are used to prevent blood clots in patients at risk of thrombosis.

The commercial formulations of heparin are sourced from porcine intestinal mucosa or from the lungs and/or intestines of cows[39]. Once isolated, this form is called unfractionated heparin (UFH). UFH can then be further processed through chemical or enzymatic cleavage to form shorter chains termed low molecular weight heparins (LMWH). The average molecular weight of UFH is approximately 19 kDa while the average molecular weight of LMWHs ranges from 3.5-6 kDa[39]. The half-life of unfractionated heparin varies from 0.5-2.5 hours, whereas the half-lives of LMWHs are longer (Table 1.1)[40–42].

Heparin is cleared from the blood through a combination of saturable and non-saturable elimination mechanisms[43,44]. The saturable mechanisms occur via clearance by the reticuloendothelial system as well as through endothelial cells[43]. The non-saturable mechanisms occur primarily through renal excretion. The contribution of these two mechanisms to heparin clearance is both dose and molecular weight dependent. The saturable mechanism accounts for the majority of elimination of the higher molecular weight fractions found with UFH[43]. The lower molecular weight fractions are primarily removed by the non-saturable renal mechanism; and thus, LMWHs half-lives become prolonged, and particularly so in those with renal insufficiency [41,43–47].

Figure 1.1: Main repeating unit structure of heparin polymer



2-O sulfonated d-iduronic acid and 6-O sulfated N sulfated d-glucosamine are the main repeating units of the heparin polymer.

Table 1.1: Pharmacokinetic properties of individual heparins

Heparin type	Biological half-life (hours)	Mean molecular weight (kDa)	Anti-Xa : thrombin activity ratio[48]
UFH	0.5 - 2.5[46]	19[39]	1 : 1
Dalteparin	2 - 4[40]	5.7[49]	1.9-3.2 : 1
Enoxaparin	4 - 5[41]	4.2[44]	3.3-5.3 : 1
Tinzaparin	3.9[42]	4.5[44]	1.5-2.5 : 1
Bemiparin	5.3[48]	3.6[48]	8.0 : 1

Abbreviations: Da = Daltons, UFH = unfractionated heparin.

1.3.2 Anticoagulant Properties of Heparin

When the endothelium of blood vessels is damaged the coagulation cascade is activated to achieve hemostasis. The coagulation cascade consists of a series of serine proteases which result in the activation of prothrombin (factor II) to thrombin (factor IIa) whose primary activity is to then convert fibrinogen (factor I) to fibrin (factor Ia) (Figure 1.2). When bound to calcium, fibrin becomes crosslinked by Factor XIII and acts as a mesh that holds platelets together forming a blood clot[50,51].

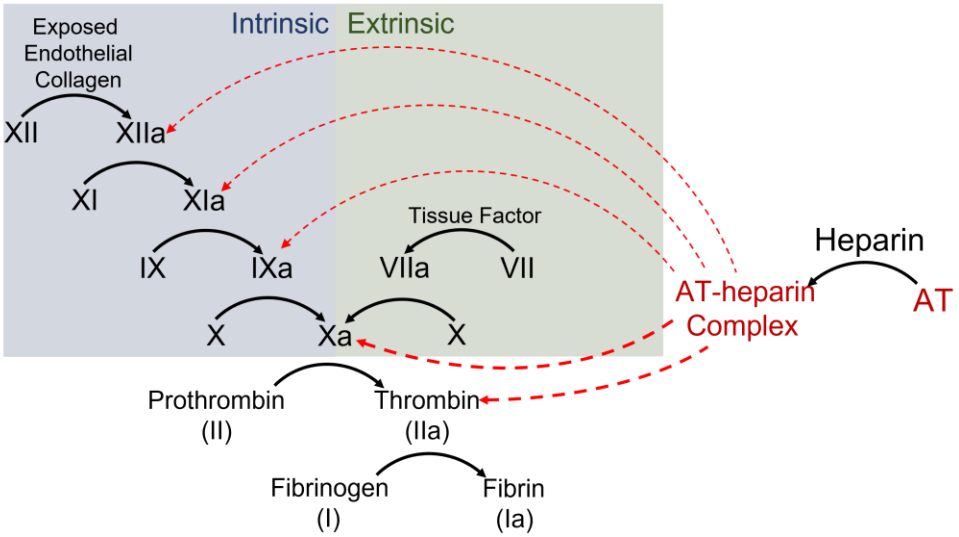
To prevent uncontrolled coagulation, the coagulation cascade has several points of regulation. One mechanism operates via antithrombin, a natural anticoagulant that inactivates several serine proteases in the coagulation cascade [50,51]. Antithrombin is a protein with an amino acid sequence that mimics the substrate of serine proteases and when cleaved covalently binds to the serine protease inactivating it. Antithrombin works by irreversibly binding to thrombin (factor IIa) and factor Xa, and to a lesser extent factors IXa, XIa, and XIIa. The inactivation of these enzymes effectively halts fibrin formation.

Antithrombin has a secondary site which, when bound to negatively charged glycosaminoglycans, can increase the inhibition of thrombin 1000-fold[50,51]. When bound, the glycosaminoglycan induces a conformational change in antithrombin which improves the protein-ligand fit, and also exposes a site on antithrombin at which thrombin and factor Xa will irreversibly bind to[50,51]. Heparan sulfate, a glycosaminoglycan found on the surfaces of human endothelial cells is one such molecule. Commercially produced heparins are similar in structure to heparan sulphate and share this ability to bind to antithrombin. Thus, through the activation of antithrombin, heparin acts as a potent anticoagulant[50,51].

Factor Xa is the serine protease that converts prothrombin (II) to thrombin (IIa) [50]. In contrast to thrombin, it is molecularly inhibited by antithrombin through a different binding mechanism. Factor Xa binds to a specific site on antithrombin-heparin complex that thrombin does not interact with. However, thrombin can interact with the heparin chain that is bound to the antithrombin-heparin complex. For thrombin to bind to the antithrombin-heparin complex the heparin chain length must be at least 13 monosaccharides (approximately 5.4 kDa). Heparin chains shorter than this will not inhibit thrombin to the same degree but will still inhibit factor Xa. It should be noted that the inhibition of factor Xa is partially molecular weight dependent as it does interact with heparin, though to a lesser degree than thrombin (Table 1.1). This explains some of the differences in properties between LMWHs and UFH. Higher relative anti-factor Xa activity is associated with improved safety and more complete inhibition of the coagulation cascade[52]. LMWHs, which on average have shorter chains, have higher ratios of inactivating factor Xa compared to thrombin, relative to the activities of UFH. Additionally, low-dose

heparin doses causes little to no changes in clotting tests & may result in subtherapeutic factor Xa inhibition[53,54].

Figure 1.2: Heparin and its effect on the coagulation cascade.



Abbreviations: AT = antithrombin
Heparin acts on the coagulation cascade by binding to AT. This increases the activity of AT by a factor of 1000 fold. The extrinsic pathway is activated by tissue factor via endothelial damage. The intrinsic pathway serves to amplify the enzymatic processes that result in the formation of a fibrin clot.

1.3.3 Anti-inflammatory Properties of Heparin

In addition to its anticoagulant properties, heparin has well-established anti-inflammatory properties, several of which are independent of its role as anticoagulant. Heparin acts to inhibit cytokine release from mast cells which mitigates host inflammation[55]. Heparin has also been shown to inhibit chemotaxis of immune cells to the sites of infection or injury as well as preventing leukocytes from attaching to the endothelium[27]. Heparin reduces lipopolysaccharide activation of monocytes, limiting both activation of coagulation and inflammation[56]. Heparin is a known inhibitor of leukocyte adhesion to endothelial cells in the microvasculature, which may serve to limit inflammation in sepsis[57–59]. Heparins have also been shown to reduce complement activation, serving to reduce inflammation and potentially increase red blood cell survival[60]. UFH increases plasma concentration of high-density lipoproteins in the setting of infection which can reduce oxidant induced cellular damage and reduce expression of cellular adhesion molecules[61,62].

1.3.4 Antiviral Properties of Heparin

Glycosaminoglycans, such as heparan sulphate, are common targets for pathogens as they are used to bind to and enter human cells[63]. In COVID-19, ACE2 is the major cell surface receptor that mediates viral adhesion by binding to the SARS-CoV-2 spike protein. Human heparan sulphate also binds a secondary site on the spike protein independent of ACE2 which potentiates viral entry into the cell[64]. Heparin, whose structure is similar to heparan sulphate, though more sulfonated, can also bind at this site and act as a competitive inhibitor. As demonstrated by Mycroft-West et al, heparin inhibits SARS-

CoV-2 invasion in a vero cell model[63]. Heparin binding appeared to be chain length dependent; shorter chains were not able to effectively interact with the spike protein[65] . Whether differential binding according to heparin type and chain length has clinical implications for patients with COVID-19 is unknown.

1.4 Prior Research

1.4.1 Therapeutic-dose heparin: Results from randomized trials in COVID-19

Several RCTs have investigated the effectiveness of therapeutic-dose heparin in patients infected with COVID-19 (Table 1.2).

The ACTIV-4a/ATTACC/REMAP-CAP multiplatform RCT (mpRCT) evaluated therapeutic-dose heparin compared to usual care venous thromboprophylaxis in patients hospitalized for COVID-19[10]. The primary outcome was an ordinal composite of ICU-level organ support and mortality. In the two main published trial reports, therapeutic-dose heparin improved survival without the need for ICU-level organ support in noncritically ill patients (odds ratio [OR] 1.27, 95% credible interval [CrI] 1.03-1.58, probability of superiority of treatment [PrS] 98.6%) but was not beneficial when given to critically ill patients[10,66].

The FREEDOM COVID trial randomized patients equally into 3 groups: 1) prophylactic-dose enoxaparin, 2) therapeutic-dose enoxaparin, 3) therapeutic-dose rivaroxaban[12]. The primary outcome was a 30-day composite of mortality, ICU level-of-care, systemic thromboembolism, or ischemic stroke. Combined therapeutic-dose rivaroxaban and enoxaparin did not appear to have a statistically significant impact on the primary 30-day outcome (hazard ratio[HR] 0.85, 95% confidence interval [CI] 0.69-1.04, p-value 0.11) In the subgroup analysis, therapeutic-dose enoxaparin (without rivaroxaban) was associated with numerical clinical improvement but this failed to reach statistical significance (HR 0.80, 95% CI, 0.63-1.02, p-value 0.07), however there was a significant improvement in mortality at 30 days (HR 0.69, 95% CI 0.49-0.98, p-value, 0.04).

The RAPID trial compared therapeutic-dose heparin to usual care venous thromboprophylaxis and did not identify a difference in the primary composite outcome of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or ICU admission, up to 28 days[67]. However, a reduction in mortality at 28 days was demonstrated in patients who received therapeutic-dose heparin (OR 0.22, 95% CI 0.07-0.65, p-value 0.006).

The HEP-COVID trial compared therapeutic-dose enoxaparin to prophylactic- or intermediate-dose LMWH or UFH[11]. Investigators found a reduction in the composite outcome of venous thrombotic events, arterial thrombotic events, and death (relative risk [RR] 0.68, 95% CI 0.49-0.96, p-value 0.03). When this trial was analyzed by ICU and non-ICU strata, a clear benefit for the use of therapeutic-dose enoxaparin for the non-ICU stratum was observed (RR 0.46, 95% CI 0.27-0.81, p-value 0.004). The treatment effect was unclear in the ICU stratum.

The ACTION trial compared therapeutic anticoagulation with either rivaroxaban or enoxaparin, followed by rivaroxaban for up to 30 days to prophylactic dose enoxaparin or UFH[68]. Therapeutic anticoagulation did not improve clinical outcomes (RR 1.49, 95% CI 0.90-2.46, p-value 0.13). Rivaroxaban was administered to 90% of patients and in a subgroup analysis, a beneficial treatment effect of therapeutic-dose enoxaparin could not be excluded.

The REMAP-CAP platform trial included patients who had received therapeutic-dose heparin while noncritically ill, and once they progressed to critical illness the were randomized to either intermediate or prophylactic-dose heparin[69]. The continuation of heparin treatment arm was discontinued on April 29th, 2022, as the prespecified criterium for futility was triggered. Continuation of therapeutic-dose heparin in patients that became critically while receiving therapeutic-dose heparin when they were noncritically ill appeared harmful (OR 0.54, 95% CrI 0.26-1.21).

Table 1.2: Clinical trials that evaluated therapeutic-dose heparin in patients hospitalized for COVID-19[a]

Trial name	Population[a]	Treatment	Control	Primary Outcome	n (treatment/ control)	Effect measure (95% CI)	p-value
mpRCT (ATTACC/ ACTIV-4a/ REMAP-CAP)[10,66]	Noncritically ill	Therapeutic-dose up to day 14	Usual care venous thromboprophylaxis up to day 14	Composite of organ support-free days to day 21 & survival[b]	1171/1048	OR 1.27 (95% CrI 1.03-1.58)	PrS 98.6%
	Critically ill				534/564	OR 0.83 (95% CrI: 0.67-1.03)	PrI 95.0%
FREEDOM COVID[12]	Not requiring ICU treatment	Therapeutic-dose enoxaparin OR Therapeutic-dose rivaroxaban	Prophylactic-dose enoxaparin	30-day composite of mortality, ICU level-of-care, systemic thromboembolism, or ischemic stroke	1136[c]/1141	HR 0.80 (0.63-1.02)	0.07[c]
RAPID[67]	Hospital ward	Therapeutic-dose LMWH or UFH to day 28	Prophylactic-dose LMWH or UFH up to day 28	Composite of death, IMV, NIV, or ICU admission, up to 28 days	228/237	OR 0.69 (0.43-1.10)	0.12
HEP-COVID[11]	D-dimer >4x upper limit of normal *or* sepsis-induced coagulopathy score of ≥4	Therapeutic-dose enoxaparin for duration of hospitalization	Prophylactic- or intermediate-dose LMWH or UFH for duration of hospitalization	Composite of VTE, ATE, or death	129/124	RR 0.68 (0.49-0.96)	0.03
				non-ICU stratum:	84/86	RR 0.46 (0.27-0.81)	0.004
				ICU stratum:	45/38	RR 0.92 (0.62-1.39)	0.71
ACTION[68]	Elevated D-dimer, COVID-19 symptoms for <14 days	Therapeutic-dose rivaroxaban or enoxaparin, followed by rivaroxaban to day 30	Prophylactic dose enoxaparin or UFH	Hierarchical composite of time to death, duration of hospitalization, or duration of supplemental oxygen use through 30 days	310[d]/304	RR 1.49 (0.90-2.46)	0.13
REMAP-CAP[69]	Critically ill	Continuation of therapeutic-dose	Intermediate or prophylactic-dose	Composite of organ support-free days to day 21 & survival[β]	26/46	OR 0.54 (95% CrI: 0.26-1.21)	PrI 97.4%

Abbreviations: CI = confidence interval, CrI = credible interval, OR = odds ratio, PrI = posterior probability of inferiority of treatment, PrS = posterior probability of superiority of treatment, RR = relative risk, ACTION = Randomized Clinical Trial to Evaluate a Routine Full Anticoagulation Strategy in Patients with Coronavirus (COVID-19), ATTACC = Antithrombotic Therapy to Ameliorate Complications of COVID-19, ACTIV-4a = A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults With COVID-19, FREEDOM COVID = FREEDOM COVID Anticoagulation Strategy Randomized Trial, HEP-COVID = Systemic Anticoagulation with Full Dose Low Molecular Weight Heparin (LMWH) Vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients, RAPID = Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care, REMAP-CAP = Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia

[a]All trial populations listed were hospitalized for COVID-19 and started the randomized treatment during hospitalization.

[b]Composite ordinal outcome; higher OR signifies improved survival and reduced organ support)

[c]FREEDOM COVID randomized patients equally into 3 groups: 1) prophylactic-dose enoxaparin, 2) therapeutic-dose enoxaparin, 3) therapeutic-dose rivaroxaban. Only results for the analysis between prophylactic-dose enoxaparin and therapeutic-dose enoxaparin are depicted in this table.

[d]90% of patients received rivaroxaban

1.4.2 Heparin Type in COVID-19

Due to the differences in the properties of various commercially available heparins (e.g., molecular weight, half-life, charge), it is possible that differential treatment effects exist according to the heparin type. RCTs completed to date have not explored potential differences in treatment effect according to heparin type. Cohort studies have shown inconsistent results likely due to limited use of various heparins [70,71].

1.4.3 The Impact of Symptom Duration in Clinical Trials

Shorter or longer symptom duration prior to hospitalization may inform the rate of COVID-19 progression and, therefore, analyzing symptom duration may identify patients at risk of disease progression[72–75]. It is also possible that there exists a differential treatment effect of heparin that is dependent on duration of COVID-19 symptoms[67,68,76].

Three trials investigated how duration of COVID-19 symptoms prior to hospitalization affected the treatment effect of heparin in subgroup analyses (Table 3). In the INSPIRATION trial (intermediate-dose vs. prophylactic-dose heparin in critically ill patients admitted to an ICU) and ACTION trial (primarily rivaroxaban in hospitalized noncritically ill patients), symptom duration, when analyzed categorically, did not appear to impact treatment effects[68,76]. In the RAPID trial, 7 or more days of COVID-19 symptoms was associated with a beneficial treatment effect[67].

Table 1.3: Clinical trials that evaluated heparin treatment in patients hospitalized for COVID-19 by treatment effects according to COVID-19 symptom duration prior to hospitalization

Trial name	Population	Treatment	Control	Primary Outcome	Duration of COVID-19 Symptoms (days)		n (treatment/ control)	Effect measure (95% CI)	P-value
ACTION[68 a]	Elevated D-dimer, COVID-19 symptoms for ≤14 days	Therapeutic-dose rivaroxaban to discharge + 30 days	Prophylactic-dose enoxaparin or UFH	Composite of time to death, duration of hospitalization, or duration of supplemental O_2 to 30 days	Symptom-days prior to *randomization*	1-9	258	WR 0.81 (0.55-1.20)	n/a
						10-11	174	WR 0.87 (0.52-1.46)	n/a
						12-15	182	WR 0.84 (0.53-1.35)	n/a
INSPIRATION[76]	Admitted to ICU	*Intermediate-dose* enoxaparin	Prophylactic-dose enoxaparin	Total thrombosis, ECMO, or mortality within 30 days	Symptom-days prior to *randomization*	≤7 days	165/163	OR 1.00 (0.64-1.54)	0.47
						>7 days	68/73	OR 1.34 (0.67-2.66)	
RAPID[67]	Admitted to hospital wards	Therapeutic-dose LMWH or UFH to day 28	Prophylactic-dose LMWH or UFH to day 28	Composite of death, IMV, NIV, ICU admission, up to 28 days	Symptom-days prior to *hospitalization*	≤7 days	125/131	OR 0.97 (0.55-1.74)	0.09
						>7 days	102/101	OR 0.39 (0.16-0.95)	

Abbreviations: ECMO = extracorporeal membrane oxygenation, IMV = invasive mechanical ventilation, NIV = non-invasive mechanical ventilation, OR = odds ratio, WR = win ratio, ACTION = Randomized Clinical Trial to Evaluate a Routine Full Anticoagulation Strategy in Patients with Coronavirus (COVID-19), INSPIRATION = Intermediate-dose vs Standard Prophylactic Anticoagulation and Statin vs Placebo in ICU Patients With COVID-19, RAPID = Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care

[a]90% of patients received rivaroxaban

1.4.4 Early Reports on the Impact of Symptom Duration in COVID-19

An early report (from January 1st to February 27th, 2020) in the pandemic from Wuhan, China demonstrated that delayed hospital admission from start of symptoms was associated with increased disease severity[72]. Additionally, a report from the UK (up to May 13th, 2020) indicated that longer symptom duration prior to hospital admission was associated with increased mortality[73]. A study from 2009 which evaluated symptom duration early in the H1N1 pandemic demonstrated a similar effect whereby longer symptom duration was associated with worse clinical outcomes[74]. These reports all originated from the earliest stages of the pandemic when timing of hospital admission may have been determined by healthcare resource availability rather than patient factors. As such, whether symptom duration impacts disease progression is uncertain.

2. Rationale & Objectives

2.1 Objective #1

It is unknown whether differential treatment effects exist according to the type of heparin used to treat COVID-19. Several trials pragmatically evaluated a variety of heparins dosed specifically either as low, intermediate, or therapeutic. No trial sought to identify a difference in treatment effect by type of heparin. The large difference in properties of LMWHs and UFH, and even the differences between different types of LMWHs, could plausibly result in differential treatment effects according to the type of heparin administered.

Using the data from the ATTACC and ACTIV-4a platforms, in this objective I investigated whether a difference in treatment effect exists according to the type of therapeutic-dose heparin compared to usual care venous thromboprophylaxis.

2.2 Objective #2

Little is known about why or how COVID-19 signs and symptoms progress in a proportion of hospitalized patients, or if antecedent symptom duration prior to hospitalization impacts disease progression. Patients who rapidly progress from symptom onset to hospitalization may have different clinical characteristics than patients who have a slower or no disease progression. The duration of COVID-19 symptoms prior to hospitalization may be an important determinant of progression risk and clinical outcome.

In the ATTACC trial, the first date of COVID-19 symptoms was ascertained for enrolled patients. I evaluated the impact of COVID-19 symptom duration prior to hospital admission on disease progression to organ support and mortality.

2.3 Objective #3

Building from the statistical models and knowledge gained in Objective #2, in this final objective I evaluated potential differences in the treatment effect of therapeutic-dose heparin according to symptom duration.

Note: *This thesis seeks to explore two areas of interest. The first is the treatment effect of different types of heparins. The second is whether the number of days of COVID-19 symptoms affects progression of illness and the treatment effect of heparin. Going forward, the component of this thesis that refers to different types of heparins will be referred to as "Evaluation of Differential Treatment Effects of Heparin Type", and the component that refers to number of days of COVID-19 symptoms will be referred to as "Evaluation of the Effects of Symptom Duration on Disease Progression & Heparin Treatment".*

3. Evaluation of Differential Treatment Effects of Heparin Type

3.1 Methods

3.1.1 Hypothesis

Hypothesis #1: We hypothesized that progression to organ support and mortality differs by heparin type.

3.1.2 Population Inclusion/Exclusion Criteria

Inclusion criteria:

1. Noncritically ill patients enrolled in ATTACC or ACTIV-4a platforms of the ATTACC/ACTIV-4a/REMAP-CAP mpRCT.
    - Noncritically ill was defined as the absence of ICU-level organ support at the time of enrollment. In the trial, ICU-level of organ support was defined as the use of high flow nasal oxygen non-invasive ventilation, invasive ventilation, extracorporeal life support, vasopressors, and/or inotropes delivered in an ICU or repurposed critical care area.
2. Patients with documented heparin administration in the first calendar day after randomization (day 1) in either the treatment or control arm.

Exclusion criteria:

1. Patients without a specified type of heparin administered on day 1

3.1.3 Main Predictor

Heparin type in the treatment arm was determined by the highest recorded total dose administered on day 1. For patients who received multiple types of heparins on the first day, the drug with the higher dose category was used. Total daily doses of single types of heparins were categorized into categories of therapeutic-dose, sub-therapeutic-dose, intermediate-dose, and low-dose to allow for cross comparison of heparin types (see Appendix sections 8.1-2 for adjudication criteria,). Low-dose heparin is used interchangeably with prophylactic-dose heparin in this thesis.

3.1.4 Endpoints

The **primary endpoint** is a composite ordinal outcome of organ support and mortality[10]:

(1) Survived through index hospitalization or up to day 90, never on organ support up to day 21.
(2) Survived through index hospitalization or up to day 90, received organ support up to day 21.
(3) Death during index hospitalization through day 90.

A list of secondary endpoints and their descriptions are included in the Table 3.1.1.

Table 3.1.1: Secondary endpoints for heparin type

Endpoint	Model	Description
Survival without respiratory support (to day 28)	Ordinal model	Ordinal endpoint with three possible outcomes based on the worst status of each patient up to day 28 following randomization: 1) Survival without non-invasive or invasive mechanical ventilation (survival without respiratory support) 2) Survival with non-invasive or invasive mechanical ventilation 3) Death Note: this outcome excludes patients on high flow oxygen at baseline (n = 31, 1.7%) to evaluate a common baseline state.
Intubation (to day 28)	Dichotomous model	Receipt of invasive mechanical ventilation up to day 28.
Hospital-free days (to 28 days)	Ordinal model	Ordinal endpoint of number of days not in hospital from date of randomization to day 28.
Survival without organ support (at 28 days)	Dichotomous model	Survival free from ICU-level organ support at 28 days. Patients were not censored at hospital discharge.
Mortality (to day 90)	Dichotomous model	Mortality status at day 90 (without censoring at hospital discharge).
Major bleeding (to day 14)	Dichotomous model	Major bleeding was defined by the International Society on Thrombosis and Haemostasis criteria and was evaluated up to day 14. This endpoint was censored at day 14 to correspond with the intervention duration.
Composite of thrombosis & mortality (in hospital or to day 28)	Dichotomous model	Composite of either death and/or thrombotic event(s) (includes myocardial infarction, pulmonary embolism, ischemic stroke, and systemic arterial embolism) during hospitalization or up to day 28.

3.1.5 List of Analyses

All planned analyses are listed below in Table 3.1.2.

Table 3.1.2: List of analyses for heparin type

Endpoint	Description	Notes
Survival without organ support (primary outcome)	1° Analysis	
Survival without organ support (primary outcome)	Sensitivity Analysis	3 separate models using different groupings of heparin types: All non-enoxaparin LMWHs grouped together All LMWHs grouped together All heparins grouped together

Survival without organ support (primary outcome)	Sensitivity Analysis	Instead of heparin type in patients randomized to therapeutic-dose heparin, the main predictor variable was replaced by dose categories, as defined by the American Society of Hematology, for individual therapeutic-dose heparin types and was compared to those that had received low-dose heparin (See Appendix section 8.2 for dose categories). In this analysis therapeutic-dose heparin was defined as the combination of sub-therapeutic- and therapeutic-doses. Low-dose was defined as the combination of intermediate- and low-doses.
Organ support-free days	Sensitivity Analysis	Number of days free from ICU-level organ support up to day 21 (0-21). Patients who didn't receive organ support up to day 21 were designated 22. Patients who died by day 90 were designated -1. Patients discharged prior to day 21 were treated as alive and not having received organ support post-discharge.
Survival without organ support (to 28 days)	Sensitivity Analysis	Ordered categorical endpoint with three possible outcomes based on the worst status of each patient to day 28 following randomization: 1) Survived index hospitalization without organ support up to day 28 2) Survived index hospitalization with organ support up to day 28 3) Died during index hospitalization up to day 28.
Survival without organ support (primary outcome)	Sensitivity Analysis	The PROTECT pilot study was a pilot study for ACTIV-4a that recorded fewer variables than ATTACC and ACTIV-4a. In this analysis patients from PROTECT were excluded to evaluate if differences in trial protocols affected the primary outcome.
Survival without organ support (primary outcome)	Sensitivity Analysis	Almost 50% of UFH was used for CKD patients despite them only taking up 7% of the total study population. This analysis included an interaction variable between therapeutic-dose UFH and presence of chronic kidney disease. All LMWHs were grouped together.

Abbreviations: CKD = chronic kidney disease, LMWH = low molecular weight heparin, UFH = unfractionated heparin.

3.1.6 Analytic Model

The model used a proportional odds logistic regression within a Bayesian framework with heparin type as the main predictor.

Covariates for the model are listed in Table 3.1.3. The model was adjusted for variables that may be associated with COVID-19 or heparin treatment to mitigate potential confounding[14,77,78]. Adjustment variables included patient demographics, baseline treatments, D-dimer (a marker of thrombosis), baseline comorbidities, and treatment group.

Table 3.1.3: Covariates included in the logistic regression model for heparin type

Covariate	Categories

Age	Continuous
Sex	Female Male
Race	Asian Black First Nations or American Indian White Other Unknown
Ethnicity	Hispanic or Latinx Not Hispanic or Latinx Unknown
D-dimer category[a]	Low High Unknown
Heparin type	*Usual care venous thromboprophylaxis* *Therapeutic-dose enoxaparin* *Therapeutic-dose dalteparin* *Therapeutic-dose with other LMWH* *Therapeutic-dose UFH*
Concomitant glucocorticoid treatment at baseline	Yes No
Supplemental oxygen at baseline[b]	None Low-flow nasal cannula or face mask High flow nasal cannula Non-invasive mech ventilation Unspecified
Site	Binned in a hierarchical manner – site/country
Time in trial	Binned in a hierarchical manner – month
Immunosuppressive disease[c]	Yes No
Severe cardiovascular disease[d]	Yes No
Diabetes	Yes No
Hypertension	Yes No
CKD	Yes No

Abbreviations: CKD = chronic kidney disease, LMWH = low molecular weight heparin, UFH = unfractionated heparin.
Footnotes:
[a]High d-dimer was defined as ≥2 times the upper limit of normal. Low dimer was defined as <2 times the upper limit of normal. Upper limit of normal was defined according to local laboratory criteria.
[b]Baseline defined as closest value prior to randomization.
[c]Immunosuppressive disease was defined as acute leukemia, lymphoma, metastatic cancer, myeloma, malignancy receiving chemotherapy, autoimmune disease (e.g., Lupus, Multiple Sclerosis, rheumatoid arthritis, transplant recipient, and other immunosuppressive disease from an adjudicated list).
[d]A baseline history of heart failure, myocardial Infarction, coronary artery disease, peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic attack)

3.2 Manuscript

The following manuscript summarizes the results of the evaluation of differential treatment effects of heparin type. Supplementary results and discussion are included in section 3.S.

The effect of therapeutic-dose heparin type in the treatment of noncritically ill patients hospitalized for COVID-19: secondary analysis of a randomized controlled trial

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Abstract

Importance

Multiple randomized clinical trials have demonstrated that therapeutic-dose heparin improves clinical outcomes in noncritically ill patients hospitalized for COVID-19. It is uncertain if the impact of therapeutic-dose heparin varies according to the type of heparin administered.

Objectives

To evaluate differential treatment effects of therapeutic-dose heparin by individual heparin type.

Design

A secondary analysis of Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) and A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (ACTIV-4a) randomized controlled trials. Treatment effects were modeled using proportional odds logistic regression within a Bayesian framework.

Setting

Patients hospitalized for COVID-19 were enrolled between May 2020 and January 2021 in Brazil, Canada, Mexico, Spain, and the US.

Participants

Noncritically ill patients enrolled in the ATTACC and ACTIV-4a trial platforms with a record of heparin administration on the first day after randomization (day 1).

Intervention

Patients were randomized to either usual care venous thromboprophylaxis or therapeutic-dose heparin.

Main Outcome and Measures

The primary outcome was an ordinal measure of 1) survival without organ support, 2) survival with organ support, and 3) death.

Results

The study population consisted of 1819 patients of whom 832 were assigned to usual care venous thromboprophylaxis and 987 to therapeutic-dose heparin. Of those assigned to therapeutic-dose, 90% were administered enoxaparin (n=887), 4% dalteparin (n=41), <1% another type of low molecular weight heparin (n=8), and 5% unfractionated heparin (n=51).

The posterior probability that therapeutic-dose heparin was superior to usual care venous thromboprophylaxis was 92.5% for enoxaparin (adjusted odds ratio [OR] 1.19 95% credible interval [CrI] 0.94-1.52); 17.8% for dalteparin (adjusted OR 0.72, 95% CrI 0.36-1.50); 33.5% for other low molecular weight heparins (adjusted OR 0.74, 95% CrI 0.17-4.36), and 65.4% for UFH (adjusted OR 1.17, 95% CrI 0.57-2.57)

Therapeutic-dose enoxaparin was associated with an increase in major bleeding (adjusted OR 2.34, 95% CrI 0.87-6.85, probability of inferiority 95.3%) and decreased composite thrombosis and mortality (adjusted OR 0.74, 95% CrI 0.50-1.09, probability of superiority 93.5%). The absolute risk of major

bleeding remained low with therapeutic-dose enoxaparin (n=15/887, 1.7%) compared to usual care venous thromboprophylaxis (n=6/832, 0.7%).

Conclusion

Treatment with therapeutic-dose enoxaparin was associated with a highly probable improvement in survival without organ support and an increased, but low, risk of major bleeding. Small sample sizes for non-enoxaparin heparins limited the ability to make meaningful inferences about treatment effects.

Trial Registration

ClinicalTrials.gov Identifiers: NCT04505774, NCT04359277, NCT04372589

Manuscript

Intro/Background

COVID-19 is associated with inflammation and a hypercoagulable state[2–4]. Patients hospitalized for COVID-19 are at increased risk of thrombosis which may contribute to respiratory failure, need for intensive care unit (ICU) support, and mortality[4,5]. Several trials have demonstrated that therapeutic-dose heparin prevents disease progression, ICU-level organ support, and mortality among noncritically ill patients hospitalized for COVID-19, with a small increase in bleeding risk[10–12,67]. However, due to the variability in heparin studied, and the unique pharmacological properties of individual heparin molecules, the relative benefit of the differing heparins is uncertain.

The objective of this study is to evaluate potential differential treatment effects of therapeutic-dose heparin according to heparin type in noncritically ill patients hospitalized for COVID-19 compared with usual care venous thromboprophylaxis.

Methods

Study Design, Data Source

We performed a secondary analysis of the ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) and ACTIV-4a (A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19) platforms of a large international multiplatform randomized trial (mpRCT). The ATTACC and ACTIV-4a platforms used a common protocol to enrol noncritically ill adult patients hospitalized with COVID-19 within 72 hours of hospital admission[10]. Patients were excluded if hospital discharge was expected within 72 hours, or if patients had a clinical indication for therapeutic anticoagulation, were at high risk of bleeding, were receiving of dual antiplatelet therapy, or had a known heparin allergy including heparin-induced thrombocytopenia (see Appendix section 8.5).

Patients were randomized to either usual care venous thromboprophylaxis or therapeutic-dose heparin. Thromboprophylaxis dose, duration, and type were determined by the treating clinician as per local protocols and were categorized using guidelines from the American Society of Hematology (see Supplementary Appendix section 8.1-2). Therapeutic-dose heparin was administered according to local protocols for the treatment of acute venous thromboembolism for up to 14 days or until recovery, as defined by hospital discharge or discontinuation of supplemental oxygen for at least 24 hours.

Study Population

We included all noncritically ill patients (i.e., those not receiving ICU-level organ support) with documented heparin administration on the first calendar day post-randomization (day 1). Patients without a record of heparin administration on day 1 were excluded. ICU-level organ support was defined as the use of high flow nasal cannula, non-invasive or invasive ventilation, extracorporeal life support, vasopressors, and/or inotropes delivered in an ICU or repurposed critical care area.

Study Variables

Heparin type was adjudicated on day 1. When multiple heparin types were used, the heparin with the highest dose was used in the analyses (see Appendix section 8.2). Individual heparin types with

sample sizes less than 10 were grouped together as “Other low molecular weight heparins”(LMWH) in the analysis.

Outcome Measures

Our primary outcome was a 3-level ordinal composite of ICU-level organ support and survival. Ordinal levels were defined by 1) survival to hospital discharge or up to day 90 without receipt of ICU-level organ support up to day 21; 2) survival to hospital discharge or up to day 90 with receipt of ICU-level organ support up to day 21; and 3) death during hospitalization up to day 90. Patients discharged prior to day 21 were assumed to have survived without organ support post-discharge. Previous trial reports using these data evaluated organ support-free days to day 21 as the primary outcome [10,66].

Secondary outcomes included a 3-level ordinal composite of respiratory support and survival (to day 28) similar to the primary outcome but replaced need for ICU-level organ support with need for invasive or non-invasive mechanical ventilation. Other secondary outcomes included intubation (to day 28), hospital-free days (to day 28), survival without organ support (to day 28), mortality (to day 90), major bleeding (to day 14) as defined by the International Society on Thrombosis and Haemostasis criteria[79], and a binary composite of total thrombosis (a composite of pulmonary embolism, deep vein thrombosis myocardial infarction, ischemic stroke, and systemic arterial embolism) and in-hospital mortality (to day 28).

Statistical Analysis

The primary analysis was performed using a Bayesian proportional odds logistic regression model using noninformative priors. The model calculated the posterior probability distribution for the proportional odds ratios for individual therapeutic-dose heparin types relative to usual care venous thromboprophylaxis. The integrated nested Laplace approximation method was used to model the adjusted odds ratios (OR), 95% credible intervals (CrI), and the posterior probabilities of superiority (PrS) of individual heparin types. Analyses of secondary outcomes were performed using the same methods as the primary analysis

To limit potential confounding by indication, the model was adjusted for variables that may be associated with COVID-19 or heparin treatment[14,77,78]. The primary model was adjusted for age, sex, race, ethnicity, severe cardiovascular disease, hypertension, diabetes, chronic kidney disease, immunosuppressive disease, baseline glucocorticoid treatment, oxygen support at baseline, d-dimer category (low, high, or unknown), country, and enrollment period (in monthly intervals). Missing data was treated as “unknown” and was included as a separate category for race, ethnicity, and oxygen support at baseline variables. Pre-specified secondary outcomes and sensitivity analyses were adjusted for the same variables as the primary outcome.

A priori subgroup analyses of the ordinal primary outcome evaluated treatment effects according to age (<50, 50-70, >70 years), sex (female, male), race (Asian, Black, First Nations or American Indian, White, Other, Unknown), ethnicity (Hispanic or Latinx, not Hispanic or Latinx, unknown), cardiovascular disease (present, absent), chronic kidney disease (absent chronic kidney disease, chronic kidney disease not on dialysis, chronic kidney disease on dialysis), baseline antiplatelet treatment (receiving, not receiving), baseline glucocorticoid treatment (receiving, not receiving), baseline

respiratory support (none, low-flow supplemental oxygen, high-flow nasal oxygen, unspecified), d-dimer (high [≥2 times the upper limit of normal], low [<2 times the upper limit of normal], unknown), weight (<100 kg, ≥100 kg, unknown), and body mass index (<18.5 kg/m^2, 18.5-30 kg/m^2, ≥30 kg/m^2, unknown). Subgroup analytic models were adjusted for age, sex, d-dimer, country, and enrollment period (in monthly intervals). Analyses were not adjusted for multiple comparisons given the model was analyzed within a Bayesian framework which outputs probability statements rather than p-values for hypothesis testing and updates probability distributions which naturally incorporate the uncertainty associated with multiple testing.

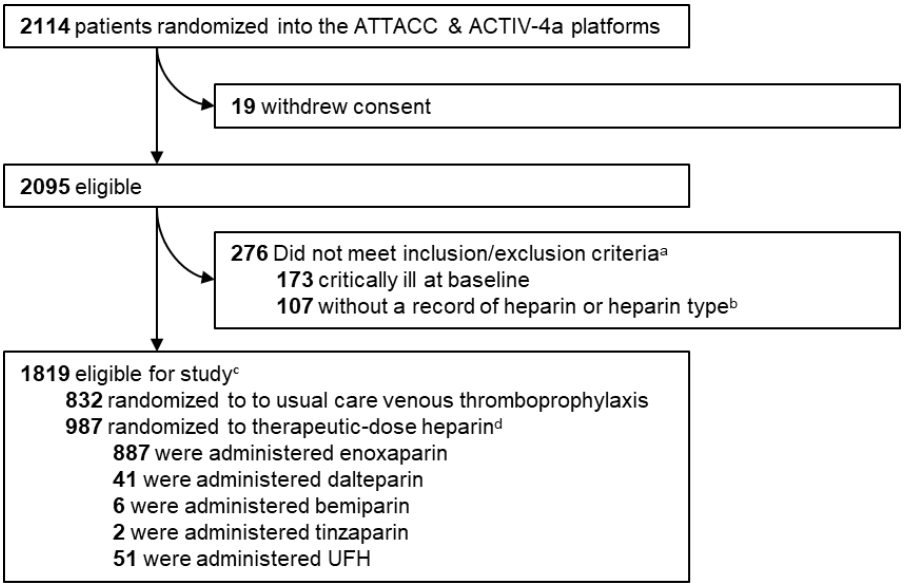
Statistical analyses were performed using R software version 4.2.3 with the integrated nested Laplace approximation package version 22.05.07.

Results

Baseline Characteristics

The ATTACC and ACTIV-4a platforms enrolled 2114 patients between May 20, 2020, and January 22, 2021, of whom 1819 met study-specific inclusion/exclusion criteria (Figure 3.2.1)[10]. Of these, 832 (46%) were assigned to usual care venous thromboprophylaxis and 987 (54%) to therapeutic-dose heparin. The mean age of the analysis cohort was 59 years (standard deviation 14 years), 41% were female, 43% identified their ethnicity as Hispanic or Latinx, and for race 18% identified as Black or African American, 9% as First Nations or American Indian, and 56% as White.

Figure 3.2.1: Study flow diagram



Abbreviations: ATTACC = Antithrombotic Therapy to Ameliorate Complications of COVID-19, ACTIV-4a = A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults With COVID-19, UFH = unfractionated heparin.

[a]Patients who were critically ill at baseline and did not have a record of heparin or heparin type are not mutually exclusive.

[b]Of the 107 patients without a record of heparin or heparin type, 67 were assigned to venous thromboprophylaxis and 40 were assigned to therapeutic-dose heparin.

[c]The difference in patients randomized to each treatment arm is due to ATTACC employing response adaptive randomization which altered the randomization ratio (1:1) at interim analyses to favour the arm benefitting patients.

[d]Type of heparin was adjudicated on the first day after randomization.

Description of Heparin Type

In the usual care venous thromboprophylaxis arm (n=832), the majority of patients received enoxaparin (88.0%) (Table 3.2.1). In the therapeutic-dose heparin arm (n=987), 89.9% (n=887) received enoxaparin, 4.2% (n=41) received dalteparin, 0.8% (n=6) received bemiparin, 0.2% (n=2) received tinzaparin, and 5.2% (n=51) received UFH. All dalteparin and tinzaparin was administered in Canada, whereas all bemiparin was administered in Spain (see Supplementary Appendix Table 3.S.1). Seventeen patients (1.7%) assigned to therapeutic-dose heparin received multiple types of heparins on day 1, all of which used UFH and one type of LMWH. Due to small sample sizes, tinzaparin and bemiparin were combined into an "other LMWHs" category and results are reported but not discussed further.

Table 3.2.1: Baseline demographics and clinical characteristics[a]

Characteristic		Usual care venous thromboprophylaxis (n=832)	Therapeutic-dose (n=987)	
			All LMWHs (n=936)	UFH (n=51)
		Number of patients (%)		
Age (years)	Mean ± SD	59 ± 14	59 ± 14	62 ± 15
Sex	Female	357 (43)	373 (40)	21 (41)
Race	Asian	34 (4)	37 (4)	0 (0)
	Black or African American	130 (16)	172 (18)	18 (35)
	First Nation/ American Indian	67 (8)	90 (10)	6 (12)
	White	488 (59)	518 (55)	20 (39)
	Other	37 (4)	40 (4)	6 (12)
	Unknown	76 (9)	79 (8)	1 (2)
Ethnicity	Hispanic or Latinx	365 (44)	414 (44)	12 (24)
	Other	447 (54)	491 (52)	39 (76)
	Unknown	20 (2)	31 (3)	0 (0)
Medical comorbidity	Severe cardiovascular disease[b]	112 (13)	93 (10)	22 (43)
	Hypertension	408 (49)	480 (51)	40 (78)
	Type 1 diabetes	15 (2)	20 (2)	2 (4)
	Type 2 diabetes	225 (27)	249 (27)	23 (45)
	CKD not on dialysis	48 (6)	43 (5)	16 (31)
	CKD on dialysis	10 (1)	2 (0)	11 (22)
	Liver disease	10 (1)	10 (1)	3 (6)
	Respiratory disease	142 (17)	162 (17)	14 (27)
	Immunosuppressive disease[c]	75 (9)	72 (8)	8 (16)
	HIV	10 (1)	8 (1)	1 (2)
Weight (kg)	Mean ± SD	89 ± 24	89 ± 24	100 ± 27
Body mass index (kg/m²)	Median (IQR)	30 (27-35)	29 (26-34)	34 (27-40)
	Obese (BMI ≥30 kg/m²)	355 (43)	369 (39)	28 (55)
Baseline treatments	Antiplatelet agent	57 (7)	63 (7)	4 (8)
	Chronic corticosteroids preadmission	64 (8)	53 (6)	7 (14)
	None	105 (13)	138 (15)	9 (18)
	Low flow nasal cannula/face mask	654 (79)	719 (77)	33 (65)

Baseline respiratory support	High flow nasal cannula	15 (2)	12 (1)	4 (8)
	Unspecified	58 (7)	67 (7)	5 (10)
Laboratory investigations (median [IQR])	D-dimer relative to site upper limit of normal	1.5 (1.0-2.7)	1.6 (0.9-2.5)	2.0 (1.4-3.8)
	Platelets x 10^9/L	217 (170-287)	218 (169-284)	201 (146-254)
	Lymphocytes x 10^9/L	0.6 (0.0-1.2)	0.7 (0.0-1.1)	0.6 (0.0-0.9)
	Creatinine (mg/dL)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	1.7 (1.3-3.6)
	eGFR (mL/min/1.73m^2)	84 (65-104)	84 (66-104)	32 (17-63)
Platform of enrollment	ATTACC	463 (56)	589 (63)	28 (55)
	ACTIV-4a	369 (44)	347 (37)	23 (45)
	PROTECT[d]	29 (3)	22 (2)	1 (2)
Country of enrollment	Brazil	194 (23)	225 (24)	2 (4)
	Canada	80 (10)	92 (10)	5 (10)
	Spain	64 (8)	58 (6)	0 (0)
	Mexico	51 (6)	71 (8)	6 (12)
	United States	443 (53)	484 (52)	38 (75)
Type of heparin administered	Enoxaparin	732 (88)	887 (95)	-
	Dalteparin	42 (5)	41 (4)	-
	Bemiparin	3 (0)	6 (1)	-
	Tinzaparin	0 (0)	2 (0)	-
	UFH	55 (7)	-	-

Abbreviations: CKD = chronic kidney disease ,eGFR = estimated glomerular filtration rate, HIV = human immunodeficiency virus, IQR = interquartile range, LMWH = low molecular weight heparin, UFH = unfractionated heparin.
[a]Supplementary Table S_ contains the demographics and baseline characteristics of individual LMWH types.
[b]Severe cardiovascular disease was defined as a baseline history of heart failure, myocardial Infarction, coronary artery disease, peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic attack [TIA]).
[c]Immunosuppressive disease includes was defined as acute leukemia, lymphoma, metastatic cancer, myeloma, malignancy receiving chemotherapy, autoimmune disease (e.g., Lupus, Multiple Sclerosis, rheumatoid arthritis, transplant recipient, and other immunosuppressive disease from an adjudicated list).
[d]The PROTECT trial was a pilot trial for the ACTIV-4a platform and is therefore a subset of ACTIV-4a.

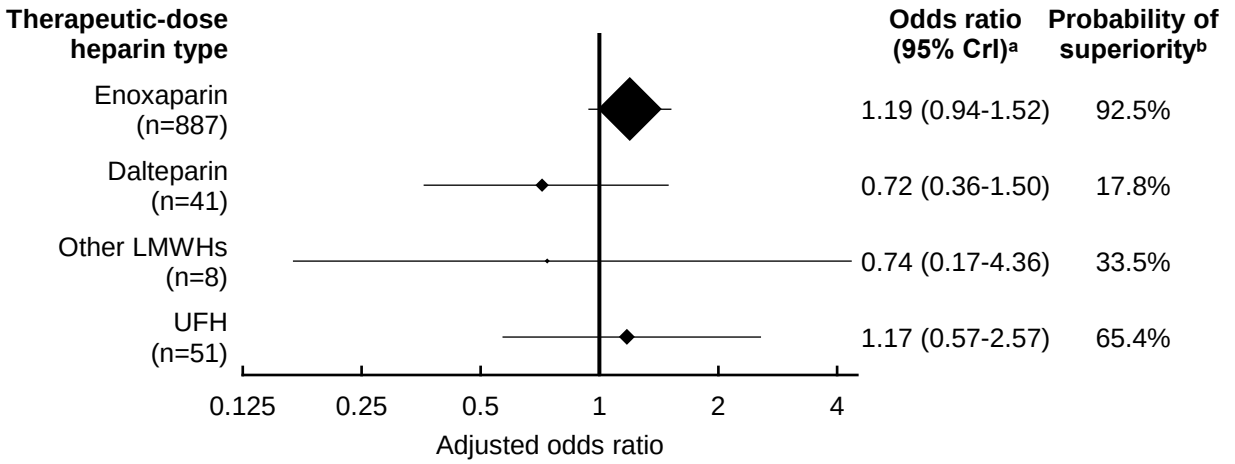
Baseline demographics were similar between patients that were assigned to usual care venous thromboprophylaxis and patients that were assigned to therapeutic-dose who received a LMWH (Table 3.2.1). In the therapeutic-dose group, patients who received UFH (n=51) had higher prevalence of medical comorbidities and obesity. Most (53%, 27/51) UFH was administered to patients with chronic kidney disease.

Obese patients who received therapeutic-dose enoxaparin received a median dose of 1.9 mg/kg/day (interquartile range [IQR] 1.7-2.0), which was similar to the weight-base dose received by non-obese patients (median 1.9 mg/kg/day, IQR 1.6-2.0) (see Supplementary Appendix Table 3.S.2).

Primary Outcome

The posterior probability that therapeutic-dose heparin was superior to usual care venous thromboprophylaxis was 92.5% for enoxaparin (adjusted OR 1.19, 95% CrI 0.94-1.52); 17.8% for dalteparin (adjusted OR 0.72, 95% CrI 0.36-1.50); and 65.4% for UFH (adjusted OR 1.17, 95% CrI 0.57-2.57) (Figure 3.2.2). Results were consistent across sensitivity analyses that evaluated variations of survival without organ support (see Supplementary Appendix Figure 3.S.1).

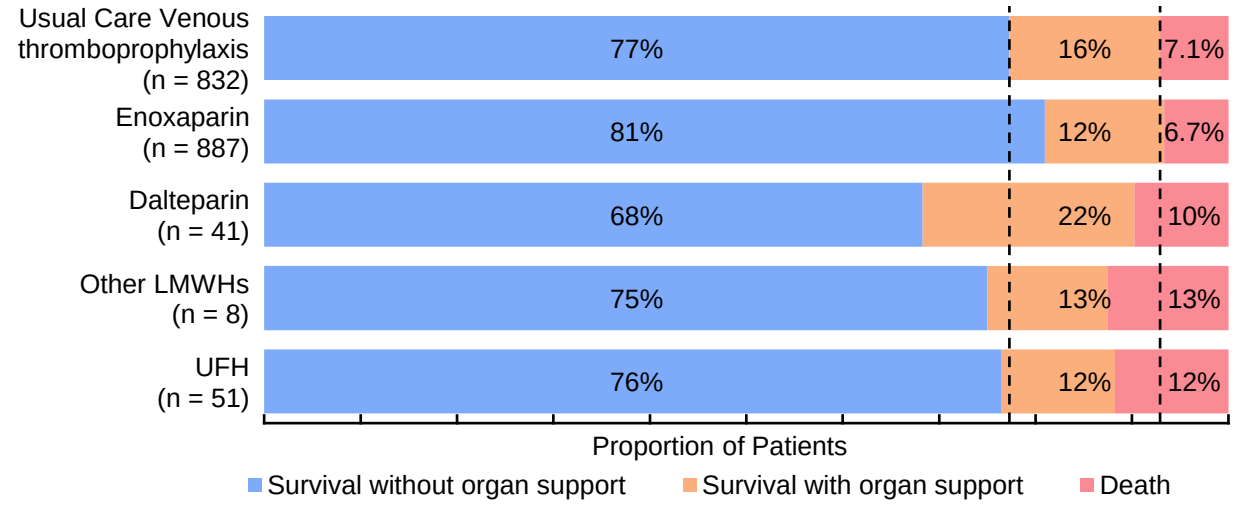
Figure 3.2.2: The effect of therapeutic-dose heparin type on survival without organ support



Abbreviations: CrI = credible interval, LMWH = low molecular weight heparin, UFH = unfractionated heparin.
[a]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 favour therapeutic-dose heparin. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis (n=832). Odds ratios adjusted for factors listed in statistical analysis.
[b]The probability of superiority is the posterior probability that an individual type of therapeutic-dose heparin is superior to venous thromboprophylaxis for improving survival without organ support.

In a descriptive comparison of the primary ordinal outcome, death during hospitalization or up to day 90 was similar among patients assigned to usual care venous thromboprophylaxis (7.1%, 59/832) compared to patients who received therapeutic-dose enoxaparin (6.7%, 59/887), and numerically less common than patients who received therapeutic-dose dalteparin (10%, 4/41) and therapeutic-dose UFH (12%, 6/51) (Figure 3.2.3). Survival with organ support to day 21 appeared less common in patients who received therapeutic-dose enoxaparin (12%, 110/887) and therapeutic-dose UFH (12%, 6/51) compared with patients who received therapeutic-dose dalteparin (22%, 9/41) and usual care venous thromboprophylaxis (16%, 130/832). Survival without organ support was numerically higher in patients receiving therapeutic-dose enoxaparin (81%, 718/887) compared to patients who received usual care venous thromboprophylaxis (77%, 643/832), therapeutic-dose UFH (76%, 39/51), or therapeutic-dose dalteparin (68%, 28/41).

Figure 3.2.3: Proportion of patients who survived without organ support, survived with organ support, and died according to heparin type

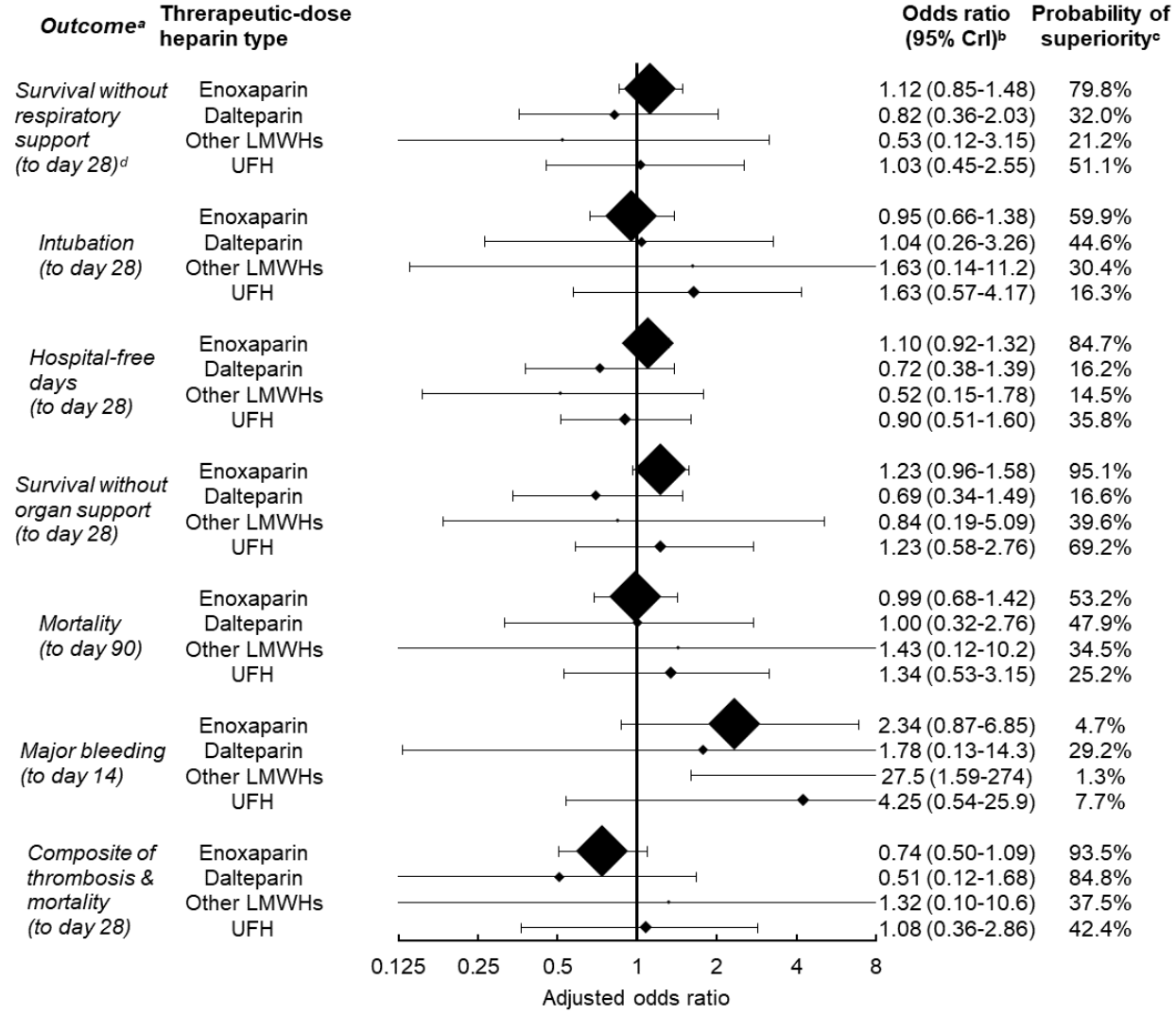


Abbreviations: LMWH = low molecular weight heparin, UFH = unfractionated heparin.

Secondary Outcomes

No heparin type was differentially associated with the composite of ICU-level respiratory support and mortality, intubation (to day 28), hospital-free days (to day 28), or mortality (to day 90) (Figure 3.2.4). Therapeutic-dose enoxaparin was the only heparin type associated with a high probability of improved survival without organ support (to day 28) (adjusted OR 1.20, 95% CrI 0.96-1.58, PrS, 95.1%) (Figure 3.2.4).

Figure 3.2.4: The effect of therapeutic-dose heparin type on secondary clinical outcomes



Abbreviations: CrI = credible interval, LMWH = low molecular weight heparin, UFH = unfractionated heparin.
[a]See Supplementary Appendix Table 3.11 for detailed descriptions of secondary outcomes.
[b]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 indicate therapeutic-dose heparin was associated with progression to the given outcome. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis (n=832). Odds ratios adjusted for factors listed in statistical analysis.
[c]The probability of superiority is the posterior probability that an individual type of therapeutic-dose heparin is superior to venous thromboprophylaxis for each respective outcome.
[d]Survival without respiratory support excluded 31 patients receiving high flow oxygen at baseline (n=1788)

Bleeding was rare among patients treated with both therapeutic- and low-dose heparin. Six patients (0.7%) experienced a major bleeding event in the usual care venous thromboprophylaxis group compared to 15 patients (1.7%) in the therapeutic-dose heparin arm (see Supplementary Appendix Table 3.S.3). There were 2 fatal bleeds, 1 in each treatment arm. Analysis of major bleeding was limited by low event rates but was likely associated with use of therapeutic-dose enoxaparin (OR 2.34, 95% CrI 0.87-6.85, PrS 95.3%).

In the usual care venous thromboprophylaxis group, 21 patients experienced a total of 24 thrombotic events, the majority of which were venous thromboembolic events (19/24, 79%) (See

supplementary Appendix Table 3.S.4). In the therapeutic-dose enoxaparin arm 14 patients experienced 18 thrombotic events with most being venous thromboembolic events (15/18, 83%). Enoxaparin was the only therapeutic-dose heparin type associated with a highly probable reduction in the composite of total thrombotic events and mortality (adjusted OR 1.40, 95% CrI 0.92- 1.98, PrS 93.5%).

Subgroup analyses

In pre-specified subgroup analyses of therapeutic-dose enoxaparin, age ≥70 years, male sex, body mass index between 18.5 and 30 kg/m^2, and absence of concomitant glucocorticoids were associated with improved survival without organ support compared to usual care venous thromboprophylaxis (see Supplementary Appendix Figure 3.S.2). Subgroup analyses related to the primary outcome for patients receiving other heparin types is presented in Supplementary Appendix Figure 3.S.4.

Discussion

In this secondary analysis of an international multiplatform trial that evaluated therapeutic-dose heparin in noncritically ill patients hospitalized for COVID-19, enoxaparin was the most common heparin administered to patients in both the usual care venous thromboprophylaxis (88%) and therapeutic-dose (89%) groups. Compared to usual care venous thromboprophylaxis, therapeutic-dose enoxaparin was the only heparin type strongly associated with improved survival without ICU-level organ support. Major bleeding was uncommon but occurred more frequently in patients who received therapeutic-dose enoxaparin compared to usual care venous thromboprophylaxis. Therapeutic-dose enoxaparin was associated with a highly probable reduction in the composite of thrombosis and mortality.

Multiple RCTs have consistently demonstrated the clinical benefit of therapeutic-dose heparin in hospitalized, noncritically ill patients with COVID-19[11,12,67]. In a meta-analysis of 6 trials that included 3297 hospitalized, noncritically ill COVID-19 patients, therapeutic-dose heparin reduced the relative risk of all-cause mortality by 24%[80]. There is little information in the literature regarding non-enoxaparin heparin types used at therapeutic-doses in the treatment of COVID-19. LMWHs have similar mean molecular weights, biological half-lives, and biological mechanisms. It is possible that treatment effects with other low molecular weight heparins would be similar to that of enoxaparin; however, the observed treatment effect of dalteparin, although inconclusive, may not support this hypothesis[44]. UFH has a higher mean molecular weight, shorter half-life, slightly different mechanisms of action, and in vitro has a greater affinity for the SARS-CoV spike protein compared to LMWHs which may elicit differential treatment effects[65]. As such, it has been suggested that the efficacy of therapeutic-dose UFH be evaluated separate from LMWHs in future trials[81].

Low molecular weight heparins are contraindicated for patients with CKD which may explain the high rates of CKD and other baseline comorbidities among patients randomized to therapeutic-dose heparin who received UFH. CKD itself is associated with higher rates of hypertension, diabetes, and cardiovascular disease[82,83]. We were unable to determine if a difference in treatment effect of UFH exists between patients with and without CKD, and thus evaluating the efficacy and safety of therapeutic-dose UFH in patients with CKD is an important objective for future trials [84].

Consistent with the results of the ATTACC/ACTIV-4a/REMAP-CAP mpRCT, in our study males experienced a greater benefit from therapeutic-dose enoxaparin compared to females. Moreover, therapeutic-dose dalteparin appeared harmful in females while it had a relatively neutral effect for males, although this analysis was limited by small subgroup sizes. In vitro studies have shown that women remain more

coagulable relative to men at increasing heparin concentrations which may explain the reduced relative benefit of therapeutic-dose that females experienced with enoxaparin[78]. Evaluating biologic sex as a potential modifier of treatment effects should be planned for in future trials of heparin.

Of patients randomly allocated to receive therapeutic-dose heparin who received enoxaparin, obese patients received a median dose of 1.9 mg/kg (IQR 1.7-2.0), and non-obese patients received a median dose of 1.9 mg/kg (IQR 1.6-2.0), yet non-obese patients differentially benefited from therapeutic-dose enoxaparin compared to obese patients. Reasons for effect modification by obesity remain to be explored but might relate to the concomitant presence of additional comorbidities in obese patients, reduced respiratory mechanics, and proclivity to thrombosis[85,86].

One of the strengths of this study is the large trial population from which it was derived. The evaluation of therapeutic-dose enoxaparin was robust given it comprised the majority of the therapeutic-dose group. Enoxaparin was administered to a diverse patient population by age, sex, race, ethnicity, comorbidities, and healthcare setting. The sample sizes of non-enoxaparin heparin groups were small, which limited the statistical inferences for heparin types. The choice of heparin-type was pragmatically left to the discretion of participating sites and, as such, differences in effect by heparin type may reflect various in patient or centre-effects rather than heparin pharmacodynamics.

Conclusion

The use of therapeutic-dose enoxaparin in noncritically ill patients hospitalized for COVID-19 improves survival without organ support, with a small increase in bleeding risk. Small sample sizes of patients treated with dalteparin, bemiparin, and tinzaparin precluded meaningful inference of differential treatment effects.

3.S Supplementary Appendix with Discussion

This section elaborates on the analysis evaluating heparin type and both includes and discusses materials referenced in the heparin type manuscript.

Table 3.2.1 from the manuscript abbreviated the individual types of LMWHs into an "All LMWHs" category. To further describe the baseline characteristics of patients, Table 3.S.1 breaks down the demographics and clinical characteristics of patients who received specific types of heparins. The individual types of heparins did not appear to systematically vary across baseline characteristics other than for UFH. Patients who received UFH had higher rates of medical comorbidities. For patients who were administered UFH, their baseline creatinine values were higher and eGFRs lower compared to the respective values of patients who received other types of heparins. The other LMWH arm consisted of 6 patients that received bemiparin in Spain and 2 patients that received tinzaparin in Canada.

Table 3.S.1: Baseline demographics and clinical characteristics by heparin type

Characteristic		Usual care venous thromboprophylaxis (n=832)	Therapeutic-dose (n=987)			
			Enoxaparin (n=887)	Dalteparin (n=41)	Other LMWH (n=8)	UFH (n=51)
		Number of patients (%)				
Age (years)	Mean ± SD	59 ± 14	59 ± 14	64 ± 15	69 ± 15	62 ± 15
	<50	211 (25)	220 (25)	5 (12)	1 (13)	12 (24)
	50-70	461 (55)	482 (54)	21 (51)	2 (25)	22 (43)
	>70	160 (19)	185 (21)	15 (37)	5 (63)	17 (33)
Sex	Female	357 (43)	350 (39)	18 (44)	5 (63)	21 (41)
Race	Asian	34 (4)	34 (4)	2 (5)	1 (13)	0 (0)
	Black or African American	130 (16)	172 (19)	0 (0)	0 (0)	18 (35)
	First Nation/ American Indian	67 (8)	81 (9)	9 (22)	0 (0)	6 (12)
	White	488 (59)	485 (55)	27 (66)	6 (75)	20 (39)
	Other	37 (4)	40 (5)	0 (0)	0 (0)	6 (12)
	Unknown	76 (9)	75 (8)	3 (7)	1 (13)	1 (2)
Ethnicity	Hispanic or Latinx	365 (44)	410 (46)	0 (0)	4 (50)	12 (24)
	Other	447 (54)	449 (51)	38 (93)	4 (50)	39 (76)
	Unknown	20 (2)	28 (3)	3 (7)	0 (0)	0 (0)
Medical History	Severe cardiovascular disease[a]	112 (13)	86 (10)	6 (15)	1 (13)	22 (43)
	Hypertension	408 (49)	457 (52)	20 (49)	3 (38)	40 (78)
	Type 1 diabetes	15 (2)	20 (2)	0 (0)	0 (0)	2 (4)
	Type 2 diabetes	225 (27)	232 (26)	15 (37)	2 (25)	23 (45)
	CKD not on dialysis	48 (6)	40 (5)	3 (7)	0 (0)	16 (31)
	CKD on dialysis	10 (1)	2 (0)	0 (0)	0 (0)	11 (22)
	Liver disease	10 (1)	10 (1)	0 (0)	0 (0)	3 (6)
	Respiratory disease	142 (17)	148 (17)	12 (29)	2 (25)	14 (27)
	Immunosuppressive disease[b]	75 (9)	68 (8)	3 (7)	1 (13)	8 (16)
	HIV	10 (1)	8 (1)	0 (0)	0 (0)	1 (2)
Baseline Treatments	Antiplatelet agent	57 (7)	54 (6)	9 (22)	0 (0)	4 (8)
	Chronic corticosteroids preadmission	64 (8)	51 (6)	2 (5)	0 (0)	7 (14)
	None	105 (13)	128 (14)	8 (20)	2 (25)	9 (18)

Baseline Respiratory Support	Low flow nasal cannula/face mask	654 (79)	681 (77)	32 (78)	6 (75)	33 (65)
	High flow nasal cannula	15 (2)	11 (1)	1 (2)	0 (0)	4 (8)
	Unspecified	58 (7)	67 (8)	0 (0)	0 (0)	5 (10)
Laboratory investigations (median [IQR])	D-dimer relative to site upper limit of normal	1.5 (1.0-2.7)	1.6 (0.9-2.5)	1.8 (1.0-3.8)	0.7 (0.5-2.1)	2.0 (1.4-3.8)
Number missing values (%)		158 (19)	169 (19)	9 (22)	1 (13)	3 (6)
	Platelets x 10^9/L	217 (170-287)	218 (169-285)	233 (197-287)	218 (163-236)	201 (146-254)
		15 (2)	16 (2)	3 (7)	0 (0)	0 (0)
	Lymphocytes x 10^9/L	0.6 (0.0-1.2)	0.7 (0.0-1.1)	0.7 (0.6-0.9)	0.0 (0.0-0.2)	0.6 (0.0-0.9)
		104 (13)	103 (12)	3 (7)	0 (0)	7 (14)
	Creatinine (mg/dL)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.8 (0.6-0.9)	0.9 (0.8-1.0)	1.7 (1.3-3.6)
		34 (4)	31 (3)	1 (2)	0 (0)	0 (0)
	eGFR (mL/min/1.73m²)	84 (65-104)	84 (66-103)	96 (74-121)	35 (33-38)	32 (17-63)
		393 (47)	367 (41)	1 (2)	6 (75)	23 (45)
Platform of Enrollment	ATTACC	463 (56)	546 (62)	41 (100)	2 (25)	28 (55)
	ACTIV-4a	369 (44)	341 (38)	0 (0)	6 (75)	23 (45)
	PROTECT[c]	29 (3)	22 (2)	0 (0)	0 (0)	1 (2)
Country of Enrollment	Brazil	194 (23)	225 (25)	0 (0)	0 (0)	2 (4)
	Canada	80 (10)	49 (6)	41 (100)	2 (25)	5 (10)
	Spain	64 (8)	58 (7)	0 (0)	6 (75)	0 (0)
	Mexico	51 (6)	71 (8)	0 (0)	0 (0)	6 (12)
	United States	443 (53)	484 (55)	0 (0)	0 (0)	38 (75)
Weight (kg)	Mean ± SD	89 ± 24	89 ± 24	88 ± 22	76 ± 17	100 ± 27
	Missing weight	55 (7)	34 (4)	4 (10)	0 (0)	6 (12)
Body mass index (kg/m²)	Median (interquartile range)	30 (35-27)	30 (34-26)	32 (33-25)	28 (30-27)	34 (40-27)
	Underweight (<18.5)	9 (1)	8 (1)	0 (0)	0 (0)	1 (2)
	18.5-<30	333 (40)	408 (46)	6 (15)	6 (75)	11 (22)
	Obese (≥30)	355 (43)	360 (41)	7 (17)	2 (25)	28 (55)
	Missing body mass index	135 (16)	111 (13)	28 (68)	0 (0)	11 (22)
Type of heparin administered	Enoxaparin	732 (88)	887 (100)	-	-	-
	Dalteparin	42 (5)	-	41 (100)	-	-
	Bemiparin	3 (0)	-	-	6 (75)	-
	Tinzaparin	0 (0)	-	-	2 (25)	-
	UFH	55 (7)	-	-	-	51 (100)

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, HIV = human immunodeficiency virus, IQR = interquartile range, LMWH = low molecular weight heparin, SD = standard deviation, UFH = unfractionated heparin.
[a]Severe cardiovascular disease was defined as a baseline history of heart failure, myocardial Infarction, coronary artery disease, peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic attack [TIA]).
[b]Immunosuppressive disease was defined as acute leukemia, lymphoma, metastatic cancer, myeloma, malignancy receiving chemotherapy, autoimmune disease (e.g., Lupus, Multiple Sclerosis, rheumatoid arthritis, transplant recipient, and other immunosuppressive disease from an adjudicated list).
[c]The PROTECT trial was a pilot trial for the ACTIV-4a platform and is therefore a subset of ACTIV-4a.

Given that dosing of heparin is primarily weight based and that dosing ceilings exist for some types of heparins, Table 3.S.2 describes the median dose, and median dose per unit body weight by heparin type and BMI. The median dose for patients who received enoxaparin in the usual care venous thromboprophylaxis arm was 40 mg for obese and non-obese patients. Obese patients who received enoxaparin in the therapeutic-dose arm received a higher dose than non-obese patients, but the median dose/kg was comparable. For the majority of patients who were administered dalteparin, BMI was

unable to be calculated due to missing data. The median dose for patients assigned to usual care venous thromboprophylaxis who received UFH was comparable between obese and non-obese patients, but the dose/kg for obese patients was lower. Obese patients assigned to therapeutic-dose heparin who were administered UFH had a higher median dose but similar doses/kg than non-obese patients. It is possible that obese patients in the therapeutic-dose arm who received therapeutic-dose enoxaparin may have received supratherapeutic-doses of heparin given studies have shown that, in patients with BMI>40 mg/kg^2, lower doses/kg are needed to achieve therapeutic anti-factor-Xa levels[85].

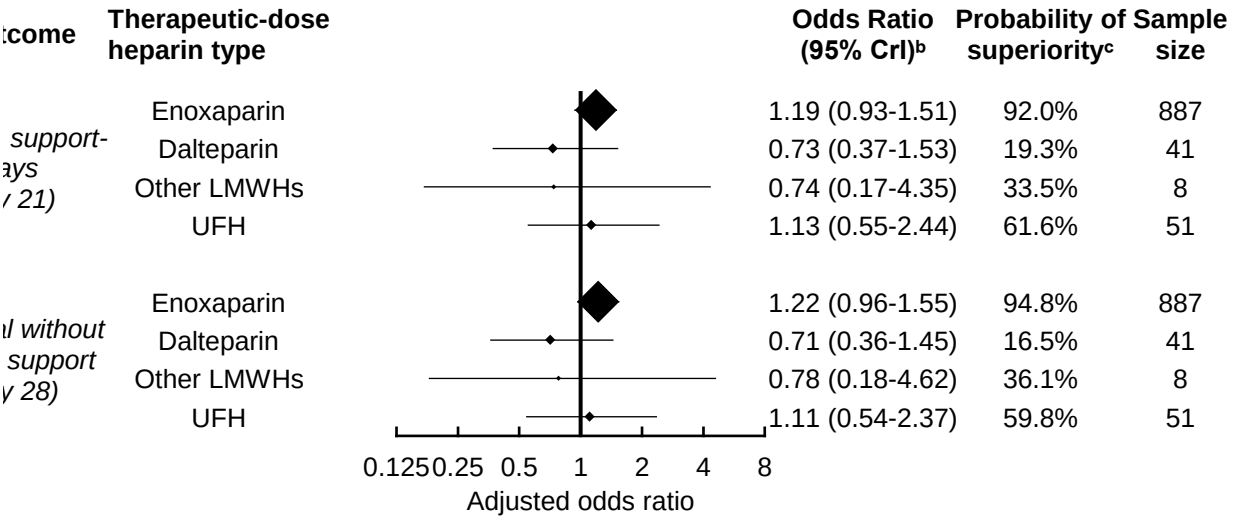
Table 3.S.2: Dosing information for each type of heparin by body mass index and treatment group[a]

Number of patients[b]						
	Enoxaparin		**Dalteparin**		**UFH**	
	Usual care venous thromboprophylaxis	Therapeutic-dose heparin	Usual care venous thromboprophylaxis	Therapeutic-dose heparin	Usual care venous thromboprophylaxis	Therapeutic-dose heparin
<30 kg/m²	286	405	10	6	27	18
Obese (≥30 kg/m²)	317	349	6	7	22	28
Unknown BMI	95	110	22	28	8	11
Median dose (IQR)						
	Enoxaparin (mg)		**Dalteparin (IU)**		**UFH (IU)**	
	Usual care venous thromboprophylaxis	Therapeutic-dose heparin	Usual care venous thromboprophylaxis	Therapeutic-dose heparin	Usual care venous thromboprophylaxis	Therapeutic-dose heparin
<30 kg/m²	40 (40-40)	140 (120-160)	5000 (5000-5000)	14200 (12725-17250)	15000 (10000-15000)	16284 (15000-30000)
Obese (≥30 kg/m²)	40 (40-80)	190 (160-220)	7500 (5625-7500)	18000 (17000-21250)	15000 (11250-22500)	30000 (15900-57938)
Unknown BMI	40 (40-63)	140 (120-160)	5000 (5000-5000)	16500 (12500-20000)	15000 (13750-15000)	15000 (15000-15000)
Median dose per unit body weight (IQR)						
	Enoxaparin (mg/kg)		**Dalteparin (IU/kg)**		**UFH (IU/kg)**	
	Usual care venous thromboprophylaxis	Therapeutic-dose heparin	Usual care venous thromboprophylaxis	Therapeutic-dose heparin	Usual care venous thromboprophylaxis	Therapeutic-dose heparin
<30 kg/m²	0.6 (0.5-0.7)	1.9 (1.6-2.0)	74 (67-94)	205 (193-213)	174 (150-211)	276 (184-375)
Obese (≥30 kg/m²)	0.5 (0.4-0.6)	1.9 (1.7-2.0)	68 (63-79)	196 (185-204)	145 (106-162)	276 (165-444)

Abbreviations: BMI = body mass index, IQR = interquartile range, IU = international units, UFH = unfractionated heparin.
[a]Dosing information for bemiparin and tinzaparin not included due to small sample sizes.
[b]Patients with adjudicated heparin type but insufficient dosing information to adjudicate heparin-specific dose category were not included in this table.

Previous publications using these data reported organ support-free days as the primary outcome[10,66]. As such, sensitivity analyses were performed using variations of the primary outcome (definitions listed in Table 3.1.2); the results were similar to the primary analysis (Figure 3.S.1).

Figure 3.S.1: The effect of therapeutic-dose heparin type on variations of the primary outcome[a]



[a]See Supplementary Appendix Table S__ for detailed descriptions of outcomes.
[b]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 favour therapeutic-dose heparin. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis (n=832). Odds ratios adjusted for factors listed in statistical analysis.
[c]The probability of superiority is the posterior probability that an individual type of therapeutic-dose heparin is superior to venous thromboprophylaxis for each respective outcome.

Bleeding events (Table 3.S.3) were more common in patients assigned to therapeutic-dose heparin for all individual types of heparins compared to usual care venous thromboprophylaxis. However, there were only 4 total events in patients that were administered dalteparin, other LMWHs, and UFH. Patients that were administered therapeutic-dose enoxaparin had over twice the incidence of major bleeding compared to usual care venous thromboprophylaxis, which is consistent with the result of the analysis of major bleeding (Figure 3.2.4).

Table 3.S.3: ISTH major bleeding events[a]

Category		Usual care venous thromboprophylaxis (n=832)	Therapeutic-dose (n=987)			
			Enoxaparin (n=887)	Dalteparin (n=41)	Other LMWHs (n=8)	UFH (n=51)
Number of patients with a bleeding event Percent (95% CrI)		6 0.7% (0.3-1.6)	15 1.7% (1.0-2.8)	1 2.4% (0.6-12.6)	1 12.5% (2.8-48.2)	2 3.9% (1.2-13.2)
	Bleeding event breakdown					
Number of	Overt bleeding causing a fall in hemoglobin ≥ 2 g/dL or leading to transfusion of ≥ 2 units of whole blood or red cells	10	19	2	1	2

Overt and symptomatic bleeding in a critical area or organ[b]	1	6	1	1	0
Fatal bleeding	1	1	0	0	0

[a]Includes all major bleeding events up to 90 days post randomization. Bleeding events were adjudicated in a blinded fashion by a separate committee using criteria from the International Society on Thrombosis and Haemostasis for major bleeding in non-surgical patients (see Appendix section 8.4). Bleeding event criteria were not mutually exclusive.
[b]Under "overt and symptomatic bleeding in a critical area or organ" only retroperitoneal bleeding was observed.

Thrombosis was more common in patients assigned to usual care venous thromboprophylaxis compared to any individual type of therapeutic-dose heparin. The lower incidence of thrombosis in patients that were administered enoxaparin compared to venous thromboprophylaxis is consistent with the analysis of composite thrombosis and mortality (Figure 3.S.5). Patients in the therapeutic-dose heparin arm who were administered dalteparin, other LMWHs, and UFH did not experience thrombosis. VTEs were more common than arterial events in both treatment groups.

Table 3.S.4: Thrombotic events during index hospitalization

Category		Usual care venous thromboprophylaxis (n=832)	Therapeutic-dose (n=987)			
			Enoxaparin (n=887)	Dalteparin (n=41)	Other LMWH (n=8)	UFH (n=51)
Number of patients with an in-hospital thrombotic event Percent (95% CrI)		21 2.5% (1.7-3.8)	14 1.6% (0.9-2.6)	0 0% (0.1-8.4)	0 0% (0.3-33.6)	0 0% (0.0-6.8)
Thrombotic Events breakdown						
Number of Events	All thrombotic events	24	18	0	0	0
	All venous thromboembolic events	19	15	0	0	0
	Pulmonary embolism	11	8	0	0	0
	Deep vein thrombosis	8	7	0	0	0
	All arterial events	5	3	0	0	0
	Myocardial infarction	1	0	0	0	0
	Ischemic cerebrovascular event (stroke)	1	1	0	0	0
	Systemic arterial thromboembolism	3	2	0	0	0

Abbreviations: CrI = credible interval, LMWH = low molecular weight heparin, UFH = unfractionated heparin.
[a]Includes all thrombotic events that occurred in hospital up to day 90. Thrombotic events were adjudicated in a blinded fashion by separate committees using consensus criteria (see Appendix section 8.3). Thrombotic events were not mutually exclusive.

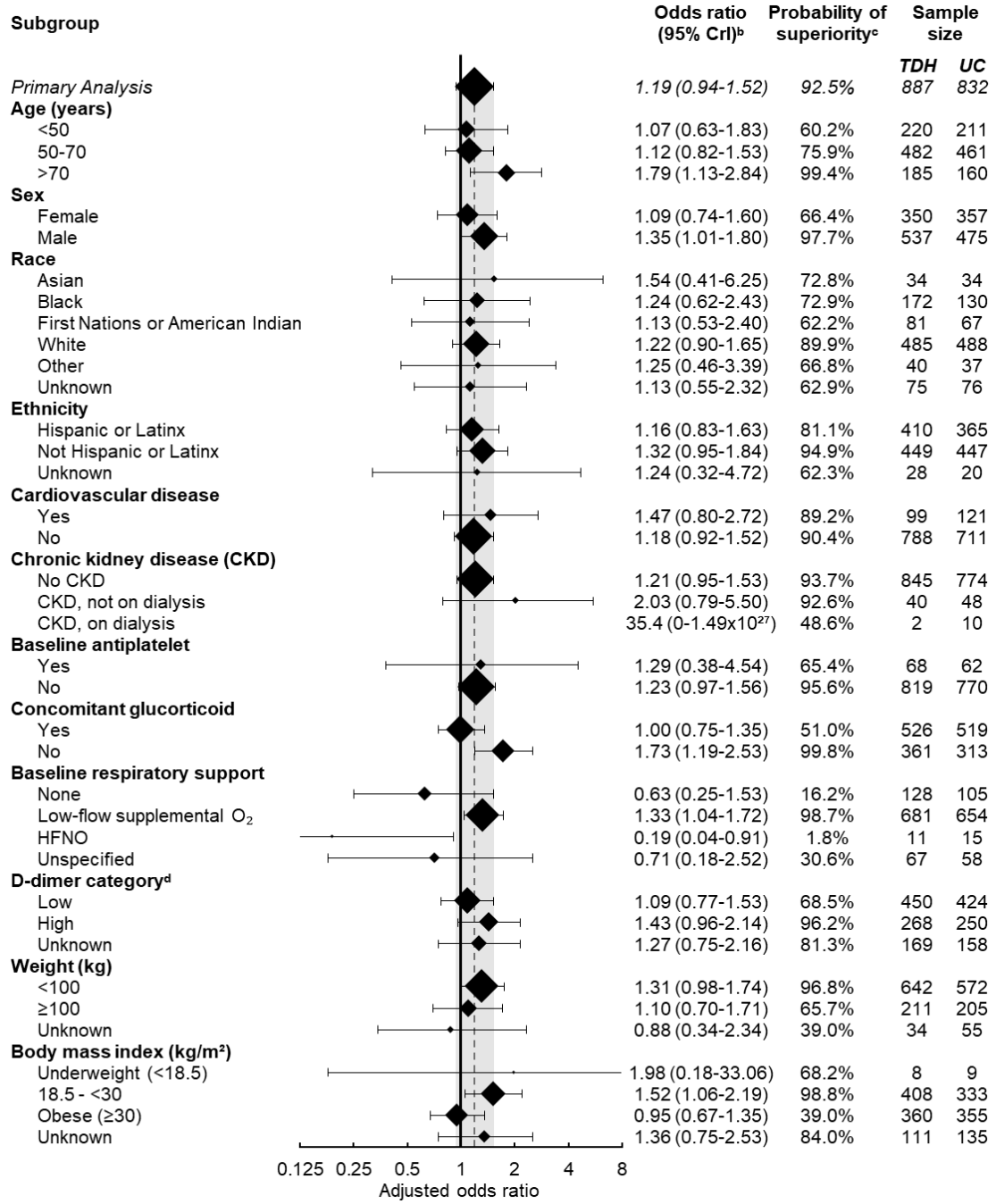
As the treatment effects of heparins may not have been consistent for all characteristics, subgroup analyses were performed (Figures 3.S.2-4).

Compared to usual care venous thromboprophylaxis, in patients who received therapeutic-dose enoxaparin, there appeared to be a greater benefit for males compared to females (Figure 3.S.2). The treatment effect of therapeutic-dose enoxaparin appeared to be greater in older patients (≥70 years compared to 50-70 years and <50 years), those not receiving glucocorticoids at baseline (compared to those receiving glucocorticoids), patients with weights <100 kg (compared to patients with weights ≥100 kg), and patients with body mass indices of ≥18.5-30 kg/m^2 (compared to obese patients).

Compared to usual care venous thromboprophylaxis, males who were administered dalteparin in the therapeutic-dose arm experienced little benefit and females appeared to experience harm (Figure 3.S.3). The small subgroup sizes limited the ability of the model to detect differences in treatments for other subgroups.

Patients >70 years old that were administered who received therapeutic-dose UFH in the therapeutic-dose group, compared to usual care venous thromboprophylaxis, may have experienced a benefit relative to younger age groups (Figure 3.S.4). There may also exist benefits for patients with high d-dimer (compared to low d-dimer), patients that weighed <100 kg (compared to patients with weights ≥100 kg), and patients with body mass indices of ≥18.5-30 kg/m^2 (compared to obese patients) however, the sample sizes for all these subgroups are relatively small.

Figure 3.S.2: The effect of therapeutic-dose enoxaparin on survival without organ support by subgroup[a]



Abbreviations: CrI = credible interval, HFNO = high-flow nasal oxygen, TDH = therapeutic-dose heparin, UC = usual care venous thromboprophylaxis

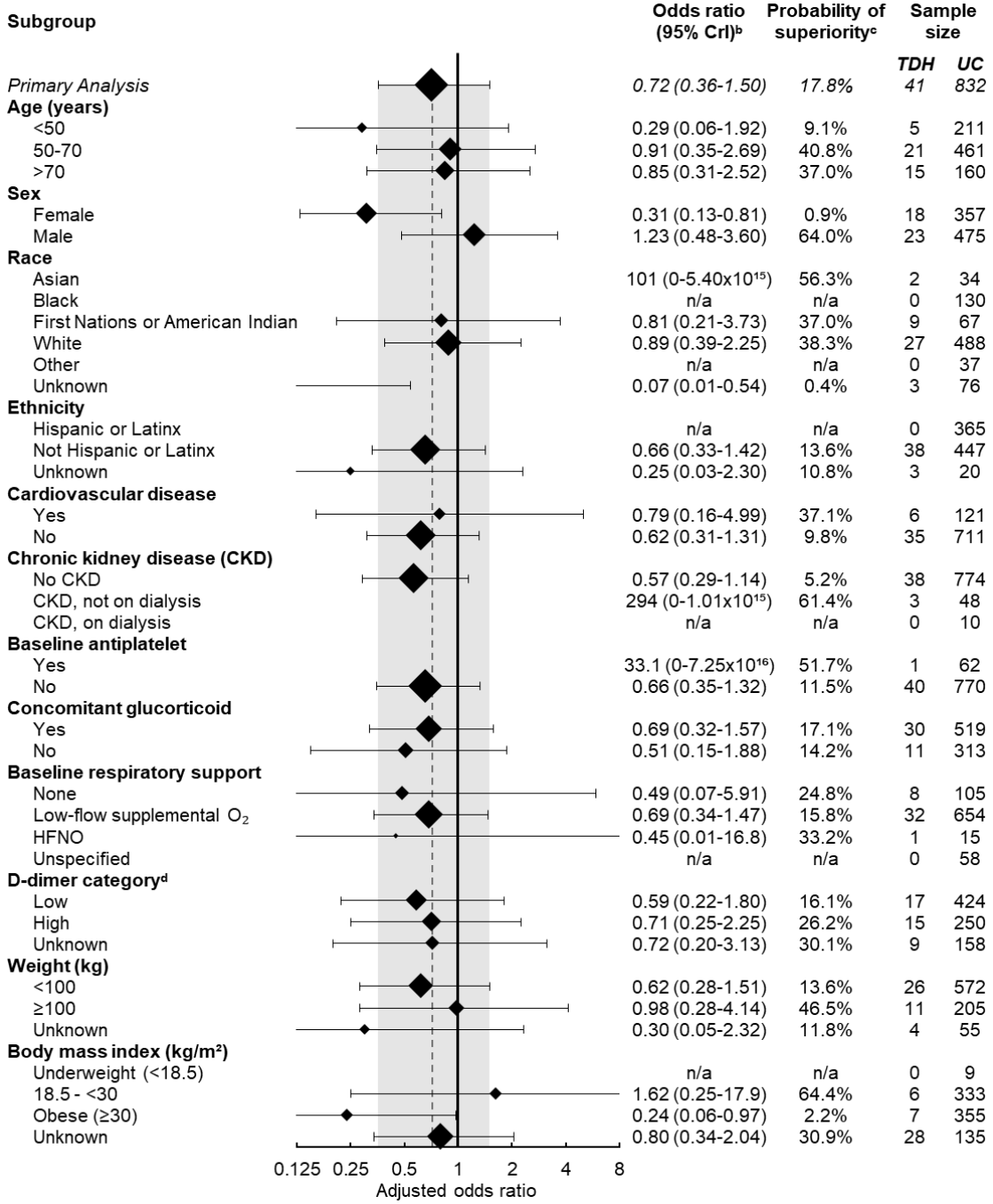
[a]Subgroup analyses were adjusted for age, sex, country, d-dimer, enrollment period (in intervals of months), and treatment group.

[b]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 favour therapeutic-dose heparin. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis. Credible interval whiskers are capped and uncapped whiskers have credible intervals that go beyond the bounds of the figure. The dark grey dashed line represents the odds ratio of the primary analysis, and the light grey area represents the 95% credible intervals. Odds ratios adjusted for factors listed in statistical analysis.

[c]The probability of superiority is the posterior probability that therapeutic-dose heparin is superior to usual care venous thromboprophylaxis for improving survival without organ support.

[d]High d-dimer was defined as ≥2 times the upper limit of normal. Low dimer was defined as <2 times the upper limit of normal. Upper limit of normal was defined according to local laboratory criteria.

Figure 3.S.3: The effect of therapeutic-dose dalteparin on survival without organ support by subgroup



Abbreviations: CrI = credible interval, HFNO = high-flow nasal oxygen, TDH = therapeutic-dose heparin, UC = usual care venous thromboprophylaxis

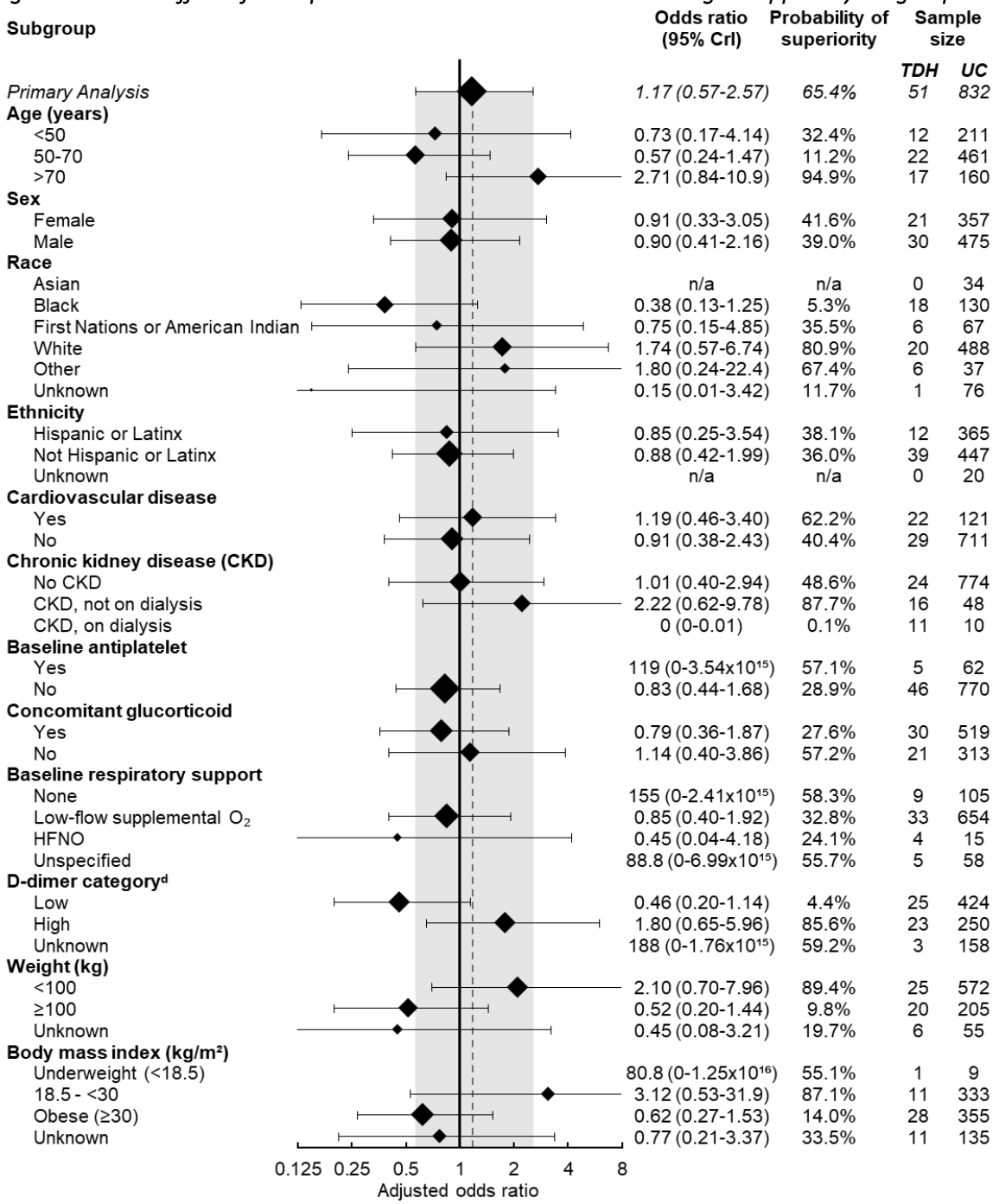
[a]Subgroup analyses were adjusted for age, sex, country, d-dimer, enrollment period (in intervals of months), and treatment group.

[b]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 favour therapeutic-dose heparin. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis. Credible interval whiskers are capped and uncapped whiskers have credible intervals that go beyond the bounds of the figure. The dark grey dashed line represents the odds ratio of the primary analysis, and the light grey area represents the 95% credible intervals. Odds ratios adjusted for factors listed in statistical analysis.

[c]The probability of superiority is the posterior probability that therapeutic-dose heparin is superior to usual care venous thromboprophylaxis for improving survival without organ support.

[d]High d-dimer was defined as ≥2 times the upper limit of normal. Low dimer was defined as <2 times the upper limit of normal. Upper limit of normal was defined according to local laboratory criteria.

Figure 3.S.4: The effect of therapeutic-dose UFH on survival without organ support by subgroup



Abbreviations: CrI = credible interval, HFNO = high-flow nasal oxygen, TDH = therapeutic-dose heparin, UC = usual care venous thromboprophylaxis

[a]Subgroup analyses were adjusted for age, sex, country, d-dimer, enrollment period (in intervals of months), and treatment group.

[b]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 favour therapeutic-dose heparin. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis. Credible interval whiskers are capped and uncapped whiskers have credible intervals that go beyond the bounds of the figure. The dark grey dashed line represents the odds ratio of the primary analysis, and the light grey area represents the 95% credible intervals.

[c]The probability of superiority is the posterior probability that therapeutic-dose heparin is superior to usual care venous thromboprophylaxis for improving survival without organ support.

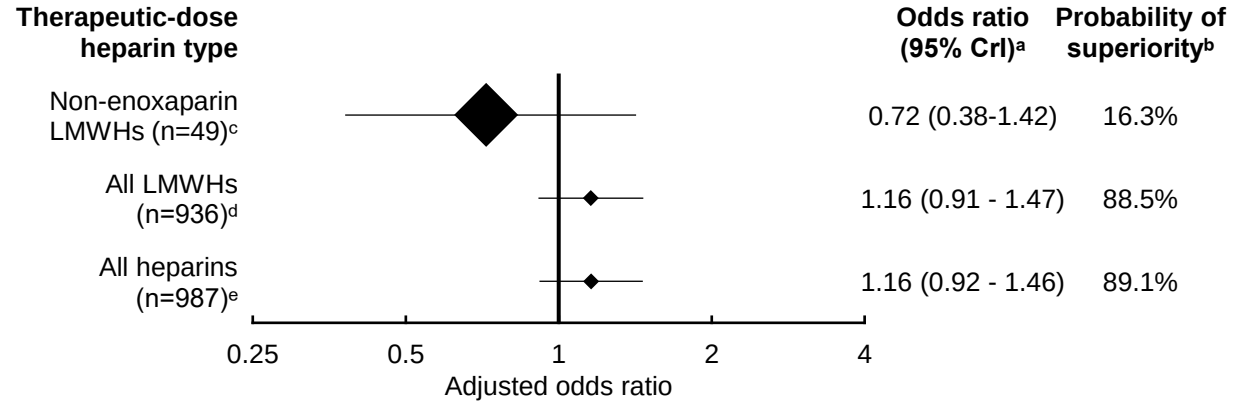
[d]High d-dimer was defined as ≥2 times the upper limit of normal. Low dimer was defined as <2 times the upper limit of normal. Upper limit of normal was defined according to local laboratory criteria

3.4 Other Figures and Tables

This section includes figures and tables of sensitivity analyses not included in the main manuscript or the supplementary appendix.

As bemiparin and tinzaparin were grouped together as "Other LMWHs", to evaluate if this affected the results, various sensitivity analyses using different groupings of heparin types were performed grouping non-enoxaparin heparins, all LMWHs, and all heparins. When non-enoxaparin LMWHs were analyzed together, the effect was similar to that of dalteparin in the primary analysis likely due to its sample size (n=41) relative to that of bemiparin (n=6) and tinzaparin (n=2). The analyses with all LMWHs grouped together and all heparins grouped together appeared very similar to the treatment effect of therapeutic-dose enoxaparin observed in the primary analysis. This similarity is likely due to the large sample size of enoxaparin which drove the treatment effects.

Figure 3.4.1: The effect of therapeutic-dose heparin type on survival without organ support with various groupings of heparin type[a]

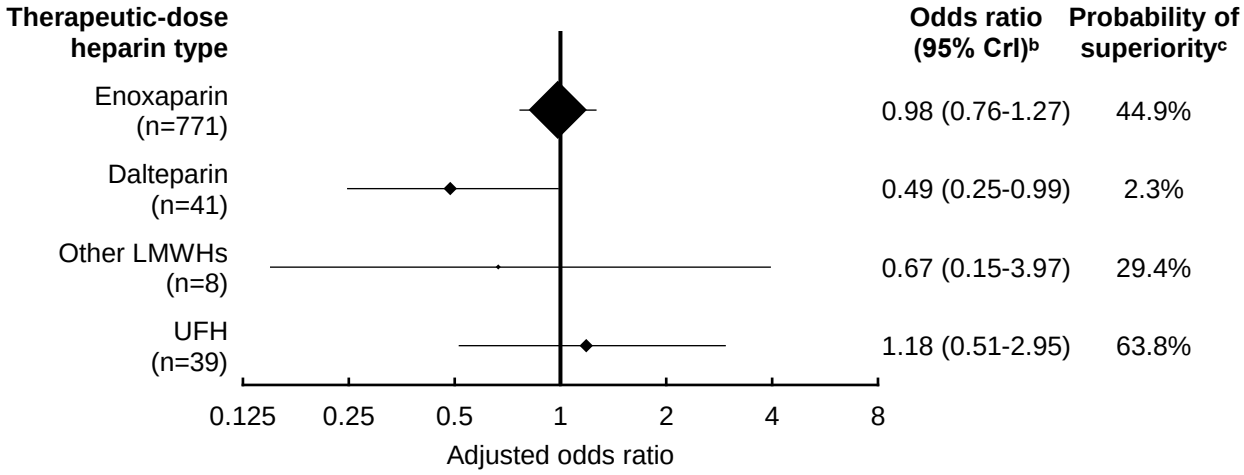


Abbreviations: CrI = credible interval, LMWH = low molecular weight heparin.
[a]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 favour therapeutic-dose heparin. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis (n=832). Odds ratios adjusted for factors listed in statistical analysis.
[b]The probability of superiority is the posterior probability that an individual type of therapeutic-dose heparin is superior to usual care venous thromboprophylaxis for each respective outcome.
[c]All patients in the therapeutic-dose arm that received a non-enoxaparin LMWH were grouped together.
[d]All patients in the therapeutic-dose arm that received a LMWH were grouped together.
[e]All patients in the therapeutic-dose arm were grouped together.

As the dose of heparin that patients received on day 1 may not have completely coincided with the treatment arm patients were assigned, an analysis using the per-protocol dose was performed. Patients were excluded (n=108) if it was not possible to adjudicate heparin dose (see appendix section 8.2 for dose adjudication details), but despite this, the low-dose (patients that received low- or intermediate-dose) heparin arm (n=852) included more patients than were randomized to usual care venous thromboprophylaxis in the primary analysis (n=832). The sample sizes of the therapeutic-dose (patients that received therapeutic- or sub-therapeutic-dose) enoxaparin and UFH groups were 13% and 23% smaller respectively than in the primary analysis. Of patients assigned to therapeutic-dose heparin,

90% of patients received a higher-dose, while patients 97% of patients assigned to usual care venous thromboprophylaxis received a lower-dose. Therapeutic-dose enoxaparin did not appear to have any benefit relative to lower-dose heparin and higher-dose dalteparin appeared harmful (Figure 3.4.2). A greater percentage of patients who received a lower-dose survived without organ support (best level of the primary outcome) in both the therapeutic-dose and usual care venous thromboprophylaxis groups (Table 3.4.1). This difference explains the difference in the treatment effects between this per-protocol analysis and the primary model as this analysis ends up concentrating patients with poor outcomes in the higher-dose group. Future studies that evaluate per protocol doses would need to accommodate for higher numbers of patients with poor outcomes being taken off treatment thus being concentrated into a single group.

Figure 3.4.2: The effect of therapeutic-dose heparin type on survival without organ support using per-protocol dose categories[a]



Abbreviations: CrI = credible interval, LMWHs = low molecular weight heparin, UFH = unfractionated heparin
[a]This analysis used per-protocol dose categories of heparin type as opposed to randomized arm by heparin type used in the primary analysis. Doses were categorized according to the American Society of Hematology guidelines (see Supplementary appendix 8.2.1).
[b]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 favour therapeutic-dose heparin. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis (n=832). Odds ratios adjusted for factors listed in statistical analysis.
[c]The probability of superiority is the posterior probability that an individual type of therapeutic-dose heparin is superior to usual care venous thromboprophylaxis for each respective outcome.

Table 3.4.1: Number of per-protocol heparin doses received by treatment arm and heparin type and number that survived without organ support

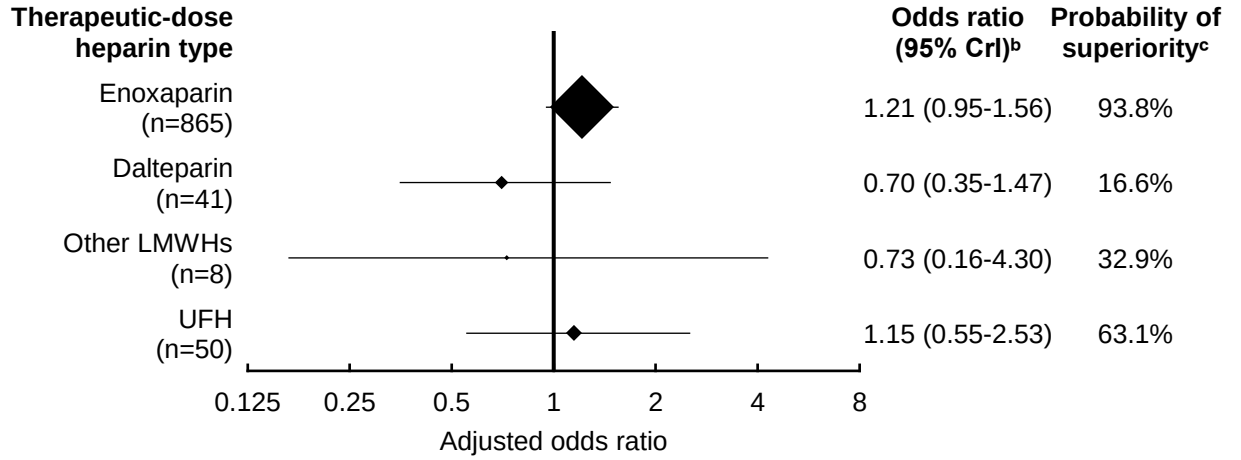
Randomized group:	**Therapeutic anticoagulation**		**Usual care venous thromboprophylaxis**	
What patients actually received[a]:	**Therapeutic- or sub-therapeutic-dose**	**Low- or intermediate-dose**	**Therapeutic- or sub-therapeutic-dose**	**Low- or intermediate-dose**
	Number of patients			
Enoxaparin	748	84	23	664
Dalteparin	39	2	2	35

Other LMWHs	8	0	0	3
UFH	39	12	0	52
Total	*834*	*98*	*25*	*754*
	Number of patients that survived without organ support (%)			
Enoxaparin	603 (81)	748 (87)	73 (57)	84 (79)
Dalteparin	26 (67)	39 (100)	2 (0)	2 (74)
Other LMWHs	6 (75)	-	-	-
UFH	30 (77)	39 (75)	-	12 (77)
Total	*665 (80)*	*834 (86)*	*84 (52)*	*98 (79)*

[a]Doses were categorized according to the American Society of Hematology guidelines (see Supplementary appendix 8.2.1).

A pilot study named PROTECT (n=52) was included in the ACTIV-4a dataset which recorded fewer data points. A sensitivity analysis was performed without PROTECT patients and the results were similar to the primary analysis (Figure 3.4.3).

Figure 3.4.3: The effect of therapeutic-dose heparin type on survival without organ support excluding PROTECT trial patients



Abbreviations: CrI = credible interval, LMWHs = low molecular weight heparin, UFH = unfractionated heparin

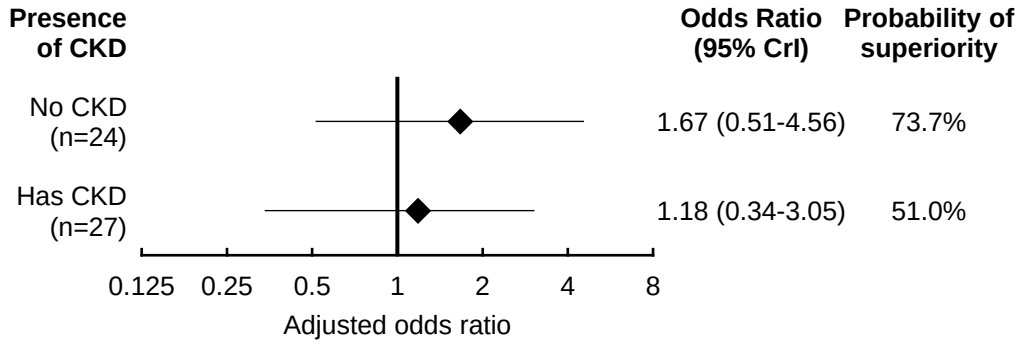
[a]The PROTECT pilot study was a pilot study for ACTIV-4a that recorded fewer variables than ATTACC and ACTIV-4a. In this analysis patients from PROTECT were excluded to evaluate if differences in trial protocols affected the primary outcome.

[b]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose group. Odds ratios >1 favour therapeutic-dose heparin. Odds ratios represent the treatment effect of therapeutic-dose heparin type relative to usual care venous thromboprophylaxis (n=832). Odds ratios adjusted for factors listed in statistical analysis.

[c]The probability of superiority is the posterior probability that an individual type of therapeutic-dose heparin is superior to usual care venous thromboprophylaxis for each respective outcome.

Over half of the UFH administered in the therapeutic-dose arm was administered to patients with chronic kidney disease, despite representing <3% of the population (Table 3.4.2). A post hoc analysis was performed with an interaction between presence of chronic kidney disease and therapeutic-dose UFH. Point estimates for the treatment effect of UFH for patients with and without chronic kidney disease likely did not differ (Figure 3.4.5).

Figure 3.4.5: The effect of therapeutic-dose UFH on survival without organ support in patients with and without chronic kidney disease[a]



Abbreviations: CKD = chronic kidney disease, CrI = credible interval, UFH = unfractionated heparin
[a]This model included an interaction variable between presence of chronic kidney disease and treatment with therapeutic-dose UFH. The odds ratios for the treatment effect of therapeutic-dose UFH are depicted by presence or lack of chronic kidney disease.
[b]The area of the odds ratio marker is proportional to the sample size of the therapeutic-dose UFH. Odds ratios >1 favour therapeutic-dose UFH. Odds ratios represent the treatment effect of therapeutic-dose UFH type relative to usual care venous thromboprophylaxis (n=832). Odds ratios adjusted for factors listed in statistical analysis.
[c]The probability of superiority is the posterior probability that therapeutic-dose UFH is superior to usual care venous thromboprophylaxis for each respective outcome.

Table 3.4.2: Heparin administration by chronic kidney disease[a]

Presence of CKD	Usual care venous thromboprophylaxis (n=796)	Therapeutic-dose	
		All LMWHs (n=908)	UFH (n=50)
	Number of patients (%)		
No CKD	738 (93)	863 (95)	23 (46)
Has CKD	58 (7)	45 (5)	27 (54)

Abbreviations: CKD = chronic kidney disease, LMWH = low molecular weight heparin, UFH = unfractionated heparin
[a]This table only includes patients with recorded presence or lack of chronic kidney disease.

4. Evaluation of the Effects of Symptom Duration on Disease Progression & Heparin Treatment

4.1 Methods

4.1.1 Hypotheses

This section explores two related hypotheses.

Hypothesis #2: In noncritically ill patients hospitalized for COVID-19, we hypothesized that progression to organ support and mortality differed by symptom duration.

Hypothesis #2b: In the same patient population, we hypothesized a difference in treatment effect of heparin by symptom duration.

4.1.2 Population Inclusion Criteria

Inclusion criteria:

1. Noncritically ill patients enrolled in the ATTACC platform of the ATTACC/ACTIV-4a/REMAP-CAP mpRCT.
    - Noncritically ill was defined as the absence of ICU-level organ support at the time of enrollment. In the trial, ICU level of organ support was defined as the use of high flow nasal oxygen non-invasive ventilation, invasive ventilation, extracorporeal life support, vasopressors, and/or inotropes delivered in an ICU or repurposed critical care area.
2. Participant study records that documented date of onset of patient-reported COVID-19 symptoms either before or on hospital admission date.

4.1.3 Main Predictor

The number of days of symptoms was obtained by taking the difference between the date of hospital admission and the date of first patient-reported COVID-19 symptoms (or date of SARS-CoV-2 PCR date for some sensitivity analyses). “Days of symptoms” will be used interchangeably with “symptom duration” to refer to the main predictor. The primary analysis for both hypotheses analyzed symptom duration as a continuous variable.

4.1.4 Endpoints

The **primary endpoint** for hypotheses 2 and 2b used a collapsed composite ordinal outcome of organ support and mortality[10]. This is the same endpoint used in the evaluation of the differential treatment effects of heparin type:

(1) Survived through index hospitalization or up to day 90, never on organ support up to day 21.
(2) Survived through index hospitalization or up to day 90, received organ support up to day 21.
(3) Death during index hospitalization through day 90.

Secondary endpoints in the evaluation of symptom duration were identical to the secondary endpoints in the heparin type manuscript (see section 3.1.4). The outcomes respiratory support and mortality, days hospitalized, and organ support and mortality (to day 28) were inverted in the manuscript to simplify interpretation (Table 4.1.1).

Table 4.1.1: Secondary endpoints pertaining to the evaluation of the effects of symptom duration on disease progression and treatment with therapeutic-dose heparin

Endpoint	Model	Description
Respiratory support & mortality (to day 28)	Ordinal model	Ordinal endpoint with three possible outcomes based on the worst status of each patient up to day 28 following randomization: 1) Survival without non-invasive or invasive mechanical ventilation (survival without respiratory support) 2) Survival with non-invasive or invasive mechanical ventilation 3) Death Note: this outcome excludes a small percent of patients on high flow nasal oxygen at baseline
Intubation (to day 28)	Dichotomous model	Receipt of invasive mechanical ventilation up to day 28.
Days hospitalized (to 28 days)	Ordinal model	Ordinal endpoint of number of days not in hospital from date of randomization to day 28.
Organ support & mortality (to day 28)	Dichotomous model	Survival free from ICU-level organ support at 28 days. Patients were not censored at hospital discharge.
Mortality (to day 90)	Dichotomous model	Mortality status at day 90 (without censoring at hospital discharge).
Major bleeding (to day 14)	Dichotomous model	Major bleeding was defined by the International Society on Thrombosis and Haemostasis criteria and was evaluated up to day 14. This endpoint was censored at day 14 to correspond with the intervention duration.
Composite of thrombosis & mortality (in hospital or to day 28)	Dichotomous model	Composite of either death and/or thrombotic event(s) (includes myocardial infarction, pulmonary embolism, ischemic stroke, and systemic arterial embolism) during hospitalization or up to day 28.

4.1.5 List of Analyses

All analyses are listed below in Table 4.1.2. The last section in Table 4.1.2 is for hypothesis 2b, all others are for hypothesis 2.

Table 4.1.2: List of analyses for symptom duration[a]

Endpoint	Description	Notes
Organ support & mortality (primary outcome)	1° Analysis (hypothesis #2)	
Organ support & mortality (primary outcome)	Sensitivity Analysis	Instead of date of symptom onset, this analysis used the difference between *date of first positive SARS-CoV-2 PCR test* and *date of hospitalization* as the main predictor variable. This analysis used both the ATTACC and ACTIV-4a data sets.
Organ support & mortality (primary outcome)	Sensitivity Analysis	For patients with symptom onset, symptom duration was obtained by taking the difference between *symptom onset* and *hospitalization*. For patients with *no symptom* onset but had a date of first positive SARS-CoV-2 PCR test, symptom duration was obtained by taking the difference between *first positive SARS-CoV-2 PCR test* and *hospitalization*. Patients with negative symptom duration values were excluded. This analysis used both the ATTACC and ACTIV-4a data sets.
Organ support & mortality (primary outcome)	Sensitivity Analysis	Symptom duration analyzed using symptom duration quartiles rather than as a continuous variable.
Organ support-free days	Sensitivity Analysis	Number of days free from ICU-level organ support up to day 21 (0-21). Patients who didn't receive organ support up to day 21 were designated 22. Patients who died by day 90 were designated -1. Patients discharged prior to day 21 were treated as alive and not having received organ support post-discharge.
Organ support & mortality (primary outcome)	Sensitivity Analysis	Instead of date of hospitalization, this analysis used the difference between date of symptom onset and date of randomization into the trial as the main predictor variable.
Organ support & mortality (to day 28)	Sensitivity Analysis	Ordered categorical endpoint with 3 possible outcomes based on the worst status of each patient to day 28 following randomization: 1) Survived index hospitalization without organ support up to day 28 2) Survived index hospitalization with organ support up to day 28 3) Died during index hospitalization up to day 28.
Organ support & mortality (primary outcome)	Sensitivity Analysis	To evaluate how age affect the effect of symptom duration on the primary outcome, this analysis included an interaction variable between symptom duration and age (both continuous variables). An additional analysis was done using age categories.
Organ support & mortality (primary outcome)	1° Analysis *(hypothesis #2b)*	To evaluate the effect of symptom duration on the treatment effect of therapeutic-dose heparin, an interaction variable between symptom duration and treatment arm was included.

[a]Symptom duration was a continuous variable for all analyses unless otherwise noted.

4.1.6 Analytic Model

The model used for hypotheses 2 and 2b were mostly identical. The models used proportional odds logistic regressions within a Bayesian framework with symptom duration as the main predictor.

Covariates for the model are listed in Table 4.1.3. To mitigate potential confounding, the model was adjusted for variables plausibly associated with COVID-19 or heparin treatment [14,77,78]. Adjustment variables included patient demographics, baseline treatments, D-dimer (a marker of thrombosis/inflammation), baseline comorbidities, and treatment group. An interaction variable between symptom duration and intervention arm was included in the statistical model used for hypothesis 2b.

Table 4.1.3: Covariates included in the logistic regression model for symptom duration

Covariate	Categories
Symptom duration*intervention arm	Interaction variable *only included in hypothesis #2b*
Age	Continuous
Sex	Female Male
Race	Asian Black First Nations or American Indian White Other Unknown
Ethnicity	Hispanic or Latinx Not Hispanic or Latinx Unknown
D-dimer category[a]	Low High Missing
Intervention Arm	*Therapeutic-dose anticoagulation* *Usual care venous thromboprophylaxis*
Concomitant glucocorticoid treatment at baseline	Yes No
Supplemental oxygen at baseline[b]	None Low-flow nasal cannula or face mask High flow nasal cannula Non-invasive mechanical ventilation Unspecified
Site	Binned in a hierarchical manner – site/country
Time in trial	Binned in a hierarchical manner – month
Immunosuppressive disease[c]	Yes No
Severe cardiovascular disease[d]	Yes No
Diabetes	Yes

	No
Hypertension	Yes
	No
CKD	Yes
	No
Symptom duration	Continuous

Abbreviations: CKD = chronic kidney disease

[a]High d-dimer was defined as ≥2 times the upper limit of normal. Low dimer was defined as <2 times the upper limit of normal. Upper limit of normal was defined according to local laboratory criteria.

[b]Baseline was defined as closest value prior to randomization.

[c]Immunosuppressive disease was defined as acute leukemia, lymphoma, metastatic cancer, myeloma, malignancy receiving chemotherapy, autoimmune disease (e.g., Lupus, Multiple Sclerosis, rheumatoid arthritis, transplant recipient, and other immunosuppressive disease from an adjudicated list).

[d]Severe cardiovascular disease was defined as a baseline history of heart failure, myocardial Infarction, coronary artery disease, peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic attack)

4.2 Manuscript for Symptom Duration

The following manuscript summarizes the main results of symptom duration. This draft has been reviewed by the MSc advisory committee but not by the larger author committee. Supplementary details and discussion are outlined in section 4.S.

The effect of symptom duration on clinical outcomes and treatment with therapeutic-dose heparin in hospitalized, noncritically ill patients with COVID-19: secondary analysis of a randomized controlled trial

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Abstract

Importance

Patients hospitalized for COVID-19 are at risk of disease progression resulting in critical illness and death. Variation in symptom duration prior to hospital admission may be associated with differential risk of disease progression and may impact the treatment effect of therapeutic-dose heparin.

Objectives

In noncritically ill patients hospitalized for COVID-19 we evaluated the influence of symptom duration prior to hospitalization on clinical outcomes and therapeutic-dose heparin treatment efficacy.

Design

We conducted a secondary analysis of the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) randomized controlled trial using proportional odds logistic regression within a Bayesian framework.

Setting

Hospitalized patients were enrolled between May 2020 and January 2021 across 60 sites in Brazil, Canada, Mexico, and the US.

Participants

Noncritically ill patients hospitalized for COVID-19, enrolled in the ATTACC trial with a documented date of COVID-19 symptom onset.

Intervention

Patients were randomized to receive either therapeutic-dose heparin or usual care venous thromboprophylaxis.

Main Outcome & Measures

The primary outcome was a 3-level ordinal composite measure consisting of 1) survival without organ support, 2) survival with organ support, or 3) death.

Results

From 1148 noncritically ill patients enrolled in the trial, we included 1137 with documented symptom onset. Of these, 638 patients were assigned to receive therapeutic-dose heparin, and 499 patients to usual-care venous thromboprophylaxis. Patients with a shorter symptom duration had higher rates of comorbidities, obesity and thrombocytopenia. Each 1 day decrease in symptoms prior to hospital admission was associated with increased progression to organ support and mortality (adjusted odds ratio 1.08, 95% credible interval 1.04-1.13, posterior probability [Pr] >99.9%). Reduced symptom duration was associated with increased respiratory support and mortality (Pr >99.9%), intubation (Pr 99.5%), days hospitalized (Pr >99.9%), 90-day mortality (Pr 99.5%), and the composite of thrombosis and death (Pr 98.2%). Therapeutic-dose heparin treatment effect estimate was not appreciably modified by symptom duration (Pr 27.2%).

Conclusion

Shorter symptom duration prior to hospital admission was associated with poor clinical outcomes in noncritically ill patients hospitalized for COVID-19. Symptom duration likely did not modify the treatment effect of therapeutic-dose heparin relative to usual care venous thromboprophylaxis.

Trial Registration

ClinicalTrials.gov Identifiers: NCT04372589

Manuscript

Intro/Background

Patients hospitalized for COVID-19 are at risk for disease progression, which can result in critical illness or death. Patients who progress to require ICU-level support are at even greater risk of mortality and more likely to experience long term health consequences. Identifying patients at risk of disease progression offers the opportunity to administer effective therapies. Patient factors such as increasing age, male sex, and the presence of diabetes, hypertension, chronic kidney disease (CKD), or obesity are individually associated with increased risk of disease progression among hospitalized patients[35–37]. It is unclear whether the duration of COVID-19 symptoms prior to hospitalization predicts disease progression and adverse clinical outcomes.

Therapeutic-dose heparin administration in noncritically ill patients hospitalized for COVID-19 has been shown to reduce disease progression, thrombotic events, and mortality in several large randomized clinical trials and meta-analyses[10–12,67,87]. It is unclear if the duration of COVID-19 symptoms prior to hospitalization modifies the clinical impact of therapeutic-dose heparin.

The objectives of this study are to 1) evaluate the effect of COVID-19 symptom duration prior to hospitalization on disease progression and mortality, and 2) evaluate the impact of symptom duration on the treatment effect of therapeutic-dose heparin.

Methods

Study Design, Data Source

We performed a secondary analysis of the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) randomized controlled trial. ATTACC enrolled adult patients hospitalized with microbiologically confirmed COVID-19 who were within 72 hours of hospital admission. The trial excluded patients who had a clinical indication for therapeutic anticoagulation, had high risk of bleeding, received dual antiplatelet therapy, or were known to have a heparin allergy including heparin-induced thrombocytopenia (HIT) (see Appendix section 8.5 for a complete list of trial exclusions).

Patients were assigned to therapeutic-dose heparin or usual care venous thromboprophylaxis. Those assigned to therapeutic-dose heparin received low molecular weight or unfractionated heparin according to local hospital policy at doses given for the treatment of venous thrombotic events (i.e., deep vein thrombosis or pulmonary embolus). The duration of treatment was to a maximum of 14 days or until patients were liberated from oxygen for 24 hours or were discharged from hospital. Pharmacologic usual care venous thromboprophylaxis was administered according to local hospital protocols. The type of heparin used in either intervention arm was determined by local clinicians and in reference to local policy and practice standards (see Appendix section 8.5).

Study Population

Our study included noncritically ill patients admitted to hospital for COVID-19 with documentation of COVID-19 symptom onset on or prior to hospital admission. Non critically ill patients comprised those admitted to hospital but did not require ICU-level organ support at the time of enrollment. ICU-level organ support was further defined as the use of high flow nasal oxygen, non-invasive or invasive ventilation, extracorporeal life support, vasopressors, and/or inotropes delivered in an ICU.

Study Variables

All variables and study data were accessed through the ATTACC trial database. Symptom duration was calculated as the difference between date of first COVID-19 symptom and date of hospital admission. Date of symptom onset was collected after patients were randomized into the trial.

Outcome Measures

The primary outcome of the trial was a 3-level ordinal composite of ICU-level organ support and mortality. Ordinal levels were defined by: 1) survival to hospital discharge or up to day 90 without receipt of ICU-level organ support up to day 21; 2) survival to hospital discharge or up to day 90 with receipt of ICU-level organ support up to day 21; or 3) death during hospitalization up to day 90. Patients discharged prior to day 21 were assumed to have survived and to have not received organ support post-discharge.

Secondary outcomes included a 3-level ordinal composite of respiratory support and mortality (to day 28), intubation (to day 28), days hospitalized (to day 28), organ support and mortality (to day 28), mortality (to day 90), major bleeding (in hospital, to day 14) as defined by the International Society on Thrombosis and Haemostasis, and a binary composite of total thrombosis (a composite of pulmonary embolism, deep vein thrombosis, myocardial infarction, ischemic stroke, and systemic arterial embolism) or mortality (in hospital, to day 28)[79].

Statistical Analysis

The primary analytic model used a Bayesian proportional odds logistic regression model with noninformative priors. The model calculated the posterior probability distribution for the proportional odds of a single day decrease of symptoms relative to usual care venous thromboprophylaxis. The integrated nested Laplace approximation method was used to model the adjusted odds ratios (adjusted OR), 95% credible intervals (95% CrI), and posterior probabilities (Pr).

To mitigate potential confounding the model was adjusted for variables plausibly associated with COVID-19 disease progression or heparin treatment[14,77,78]. The primary model was adjusted for age, sex, race, ethnicity, severe cardiovascular disease, hypertension, diabetes, chronic kidney disease, immunosuppressive disease, baseline glucocorticoid treatment, oxygen support at baseline, d-dimer category (low, high, or unknown), country, and enrollment period (in monthly intervals). The model used to evaluate the treatment effect of therapeutic-dose heparin by symptom duration included the same covariates, along with an interaction variable between treatment arm and symptom duration. Analyses of secondary outcomes and sensitivity analyses were adjusted for the same set of variables as the primary outcome.

Subgroup analyses evaluated treatment effects according to age, sex, race, ethnicity, cardiovascular disease, chronic kidney disease, baseline antiplatelet treatment, baseline glucocorticoid treatment, baseline respiratory support, d-dimer, weight, and body mass index. Subgroup analyses were adjusted for age, sex, d-dimer, country, and enrollment period (in monthly intervals).

A sensitivity analysis was performed using the difference between date of first COVID-19 symptom and randomization date. Additional sensitivity analyses were performed with the combined population of ATTACC and ACTIV-4a trial platforms (A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults With COVID-19) using the difference between date of first positive SARS-CoV-2 PCR test and date of hospitalization.

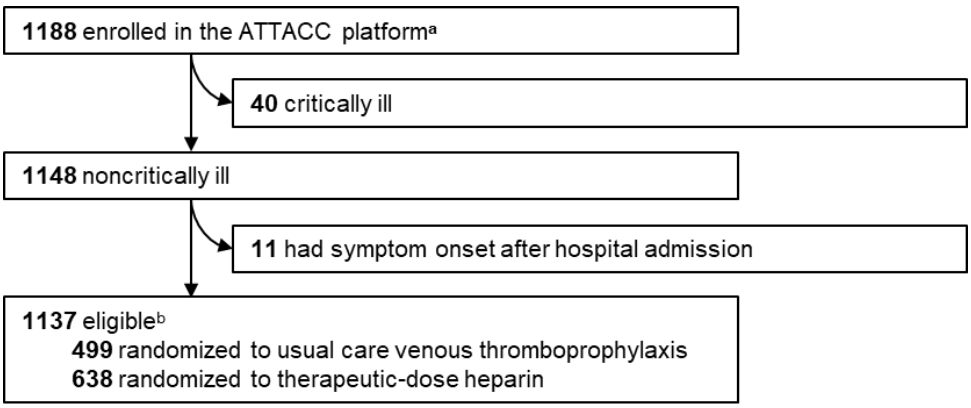
Statistical analyses were performed using R software version 4.2.3 with the integrated nested Laplace approximation package version 22.05.07.

Results

Baseline Characteristics

Screening, enrollment, and randomization within the ATTACC trial was previously reported[10]. We included 1137 of the 1148 noncritically ill patients enrolled from May 20, 2020 to January 22, 2021, (Figure 4.2.1). The mean age was 58 years (standard deviation [SD] 14 years); 42% (472/1137) were female. Thirty-eight percent (38%) of patient were enrolled in Brazil, 33% in the US, 16% in Canada, and 13% in Mexico. At baseline, 76% of patients received low flow nasal oxygen, 2% received high flow nasal oxygen, and 23% were not on supplementary oxygen. Of the 1137 patients included, 56% (638/1137) were assigned to receive therapeutic-dose heparin and 44% (499/1137) were assigned to usual care venous thromboprophylaxis; unequal randomization proportions reflect the application of responsive adaptive randomization within the trial. Patient characteristics between treatment groups were similar. Enoxaparin was the most commonly administered heparin type in both the therapeutic-dose (80.0%) and usual care venous thromboprophylaxis (85.1%) groups.

Figure 4.2.1: Study flow diagram[a]

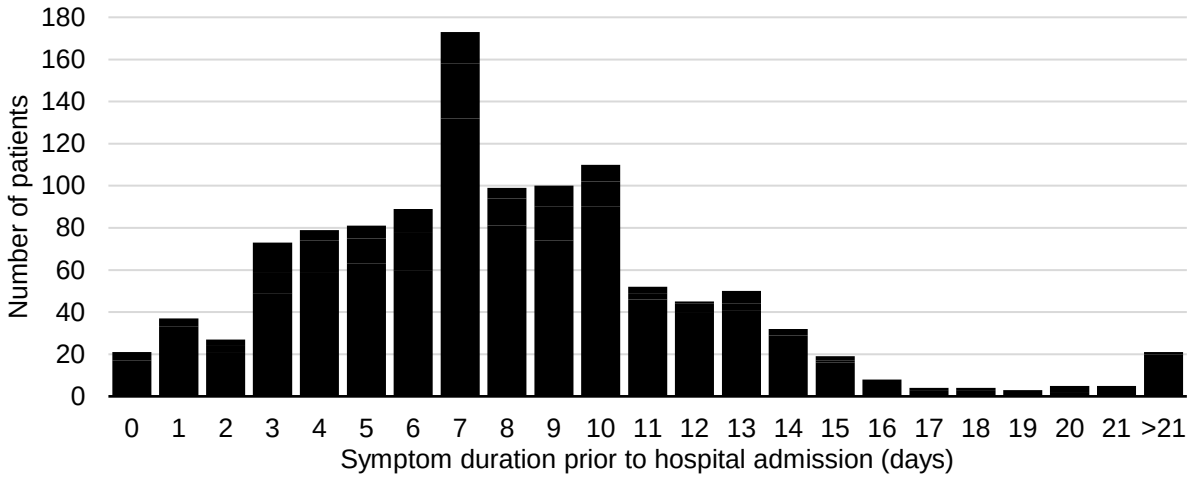


Abbreviations: ATTACC = Antithrombotic Therapy to Ameliorate Complications of COVID-19
[a]The 1188 enrolled patients do not include patients that had previously withdrawn informed consent which have been reported in Lawler et al.[10]
[b]The difference in patients randomized to each treatment arm is due to ATTACC employing response adaptive randomization which changed the randomization rate (1:1) at interim analyses to favour the arm benefitting patients.

Description of symptom duration

The mean duration of COVID-19 symptoms prior to hospital admission was 8.1 days (SD 5.1 days), and the median was 7 days (interquartile range [IQR] 5-10) (Figure 4.2.2). Females, obese patients, and those with pre-existing medical comorbidities presented to hospital with shorter symptom duration (Table 4.2.1). Patients in the shortest symptom duration quartile presented with lower platelet counts. In Canada and the US more patients presented with shorter symptom durations, whereas in Brazil and Mexico patients tended to present with longer symptom durations.

Figure 4.2.2: Distribution of symptom duration[a]



[a]Symptom duration was calculated as the difference between symptom onset and hospital admission.

Table 4.2.1: Baseline demographics

Characteristic		Symptom duration quartile			
		0-5 days [n=318]	6-7 days [n=262]	8-10 days [n=309]	≥11 days [n=248]
		Number of patients (%)			
Age (years)	Mean ± SD	59 ± 16	58 ± 15	56 ± 13	58 ± 13
Sex	Female	152 (48)	119 (45)	101 (33)	100 (40)
Race	Asian	4 (1)	11 (4)	15 (5)	6 (2)
	Black	90 (28)	64 (24)	34 (11)	33 (13)
	First Nations or American Indian	40 (13)	32 (12)	52 (17)	42 (17)
	White	155 (49)	136 (52)	185 (60)	149 (60)
	Other	22 (7)	10 (4)	20 (6)	17 (7)
	Unknown	7 (2)	9 (3)	3 (1)	1 (0)
Ethnicity	Hispanic or Latinx	121 (38)	113 (43)	203 (66)	162 (65)
	Not Hispanic or Latinx	192 (60)	144 (55)	102 (33)	82 (33)
	Unknown	5 (2)	5 (2)	4 (1)	4 (2)
Medical comorbidity	Severe cardiovascular disease[a]	58 (18)	30 (11)	20 (6)	18 (7)
	Hypertension	172 (54)	134 (51)	130 (42)	125 (50)
	Type 1 diabetes	12 (4)	11 (4)	5 (2)	3 (1)
	Type 2 diabetes	105 (33)	68 (26)	70 (23)	65 (26)
	CKD not on dialysis	36 (11)	7 (3)	10 (3)	8 (3)
	CKD on dialysis	5 (2)	2 (1)	1 (0)	1 (0)
	Liver disease	4 (1)	1 (0)	2 (1)	2 (1)
	Respiratory disease	62 (19)	51 (19)	34 (11)	33 (13)
	Immunosuppressive disease[b]	28 (9)	26 (10)	17 (6)	13 (5)
	HIV	6 (2)	0 (0)	2 (1)	1 (0)
Weight (kg)	Mean ± SD	93.0 ± 26.7	89.4 ± 23.1	87.8 ± 20.5	85.8 ± 20.9
Body mass index (kg/m^2)	Median (interquartile range)	30.5 (37.1-26.6)	31.2 (35.0-26.7)	29.4 (33.3-26.3)	29.0 (32.8-25.9)
	Obese (≥30)	138 (43)	120 (46)	124 (40)	95 (38)
Baseline treatments	Antiplatelet agent	44 (14)	28 (11)	26 (8)	22 (9)
	Chronic corticosteroids preadmission	13 (4)	7 (3)	7 (2)	4 (2)
Baseline respiratory support	None	98 (31)	57 (22)	52 (17)	50 (20)
	Low flow nasal cannula/face mask	216 (68)	200 (76)	249 (81)	194 (78)
	High flow nasal cannula	4 (1)	5 (2)	7 (2)	4 (2)
Laboratory investigations (median [IQR])	D-dimer (relative to upper limit of normal)	1.5 (0.8-2.7)	1.5 (0.9-2.2)	1.3 (0.8-2.2)	1.7 (1.0-3.0)
	Platelets x 10^9/L	200 (162-270)	209 (164-270)	224 (176-290)	248 (194-340)
	Lymphocytes x 10^9/L	1.0 (0.7-1.4)	1.0 (0.7-1.3)	0.9 (0.7-1.3)	1.1 (0.8-1.5)
	Creatinine (mg/dL)	0.9 (0.8-1.2)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)
	eGFR ($mL/min/1.73m^2$)	78 (58-101)	86 (69-103)	85 (70-104)	85 (67-104)
Country of enrollment	Brazil	71 (22)	86 (33)	151 (49)	124 (50)

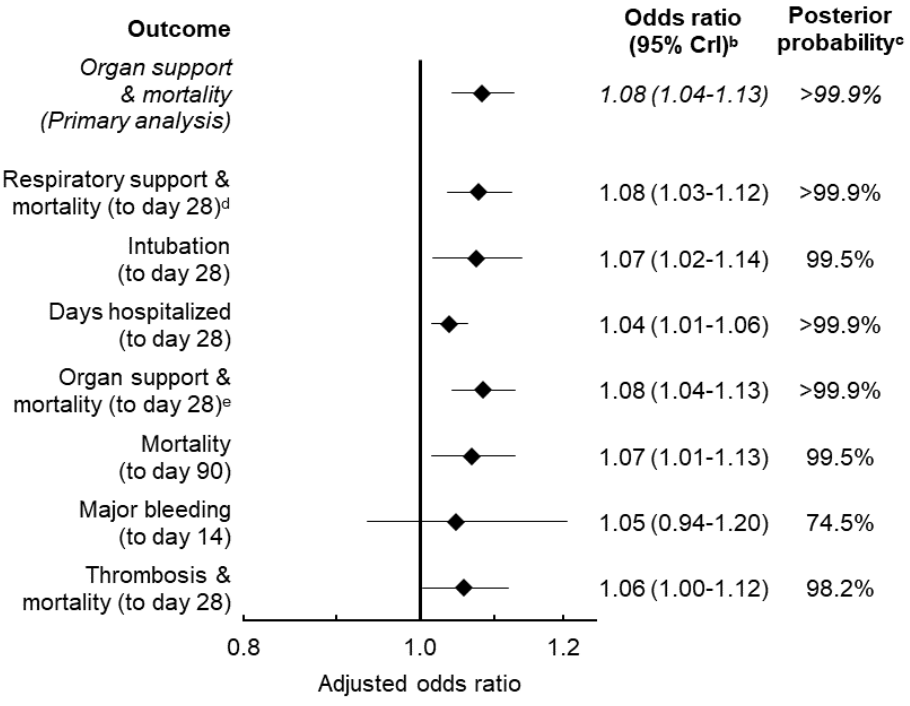
	Canada	63 (20)	51 (19)	39 (13)	30 (12)
	Mexico	37 (12)	23 (9)	50 (16)	36 (15)
	United States	147 (46)	102 (39)	69 (22)	58 (23)
Randomized treatment	Therapeutic-dose heparin	177 (56)	150 (57)	170 (55)	141 (57)
	Usual care venous thromboprophylaxis	141 (44)	112 (43)	139 (45)	107 (43)
Anticoagulant administered (on day 1)	Enoxaparin	243 (76)	216 (82)	266 (86)	217 (88)
	Dalteparin	22 (7)	26 (10)	22 (7)	12 (5)
	Tinzaparin	2 (1)	0 (0)	0 (0)	0 (0)
	UFH	25 (8)	8 (3)	4 (1)	8 (3)
	Unknown	26 (8)	12 (5)	17 (6)	11 (4)

Abbreviations: CKD = chronic kidney disease, day 1 = the day after randomization into ATTACC, eGFR = estimated glomerular filtration rate, HIV = human immunodeficiency virus, IQR = interquartile range, SD = standard deviation, UFH = unfractionated heparin.
[a]Severe cardiovascular disease was defined as a baseline history of heart failure, myocardial Infarction, coronary artery disease, peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic attack).
[b]Immunosuppressive disease was defined as acute leukemia, lymphoma, metastatic cancer, myeloma, malignancy receiving chemotherapy, autoimmune disease (e.g., lupus, multiple sclerosis, rheumatoid arthritis, transplant recipient, or other immunosuppressive diseases).

Primary Outcome

Each 1-day reduction in symptom duration prior to hospital admission (i.e. shorter symptom duration) was associated with increased ICU-level organ support and mortality (adjusted OR 1.08, 95% CrI 1.04-1.13, Pr >99.9%) (Figure 4.2.3). An analysis utilizing symptom duration quartiles yielded similar results (see Supplementary Appendix Figure 4.S.1).

Figure 4.2.3: The effect of shorter symptom duration on clinical outcomes[a]



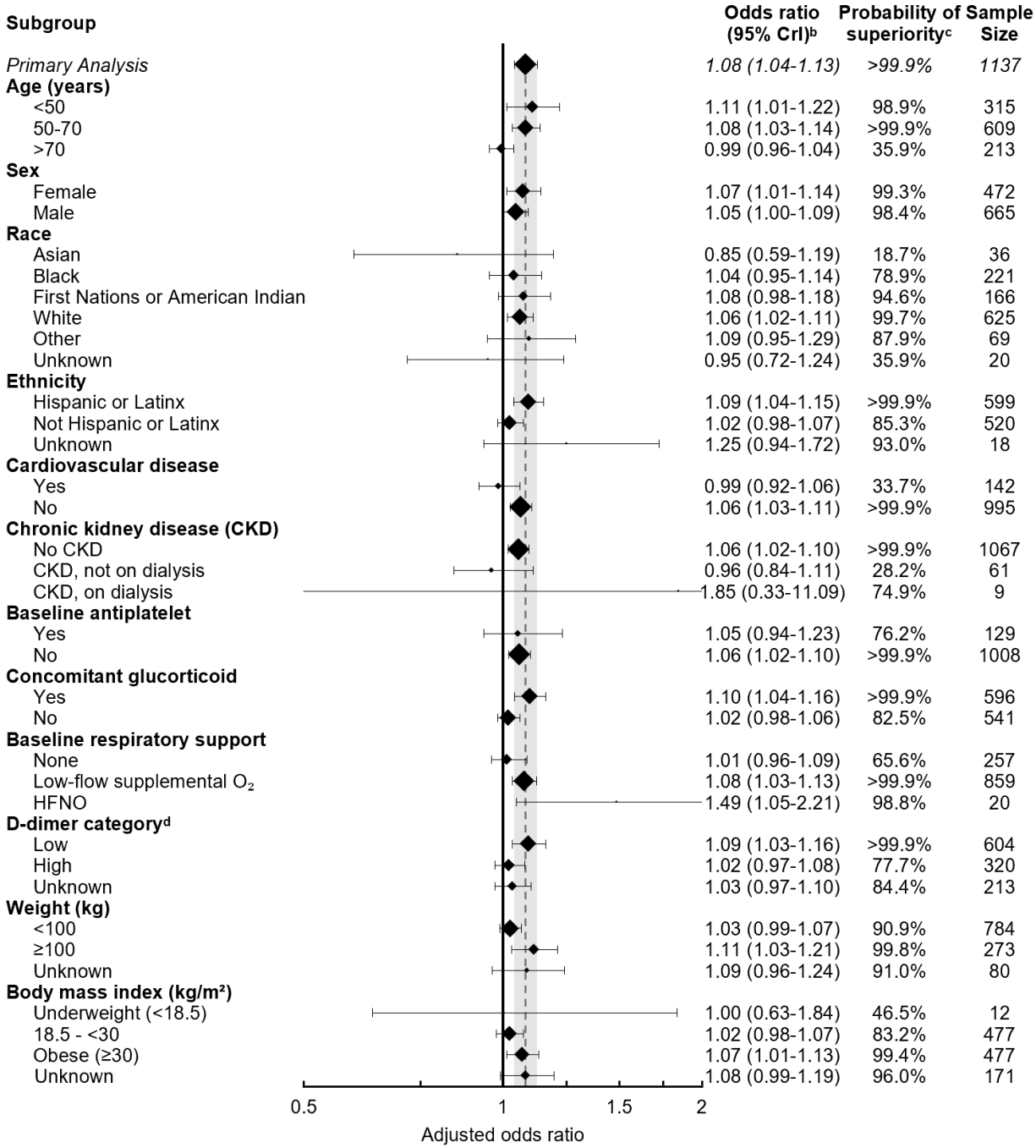
Abbreviations: CrI = credible interval
[a]See Supplementary Appendix Table 4.11 for detailed descriptions of secondary outcomes.
[b]Odds ratios represent the effect of a single day decrease in symptoms for each respective outcome. An odds ratio greater than 1 indicates increased progression or harm for a given outcome. Odds ratios adjusted for factors listed in statistical analysis.
[c]The posterior probability is the probability that a single day decrease of symptoms was associated with increased progression to a given outcome.
[d]Analysis of respiratory support and mortality excluded 20 patients receiving high flow nasal oxygen at baseline (n=1117).
[e]Organ support and mortality (to day 28) was a binary outcome separate from the primary outcome.

Each single day decrease day of symptoms was consistently associated with worse clinical outcomes across sensitivity analyses using permutations in the definition of symptom duration (e.g., symptom onset to date of randomization, or date of first positive SARS-CoV-2 test to hospitalization) as well as permutations in clinical outcomes (see Supplementary Appendix Figures 4.S.2-6 and Table 4.S.1).

Subgroup Analyses

The impact of symptom duration on ICU-level organ support and mortality varied across a number of subgroups (Figure 4.2.4). In subgroup analyses of age, symptom duration was not likely associated with progression to ICU-level organ support and mortality in patients ≥70 years old. This observation was supported by post hoc analyses that included interaction variables between symptom duration and age which demonstrated that symptom duration was likely not associated with disease progression in older patients (Pr of interaction of age*symptom duration <0.01%) (see Supplementary appendix Table 4.S.2 and Figure 4.S.7). Additionally, symptom duration appeared to have a reduced effect on progression to ICU-level organ support and mortality in patients with several characteristics including cardiovascular disease, absence of concomitant glucocorticoid treatment, patients who identif as Hispanic or Latinx, high d-dimer, and lower body weight.

Figure 4.2.4: The effect of shorter symptom duration on organ support and mortality by subgroup[a]



Abbreviations: CrI = credible interval, HFNO = high-flow nasal oxygen, CKD = chronic kidney disease

[a]Subgroup analyses were adjusted for age, sex, country, d-dimer, enrollment period (in intervals of months), and treatment group.

[b]Odds ratios represent the effects of a single day decrease in symptoms on progression to organ support and mortality. The area of the odds ratio marker is proportional to the sample size of the subgroup. Credible intervals (whiskers) are capped and uncapped whiskers have credible intervals that go beyond the bounds of the figure. The dark grey dashed line represents the odds ratio of the primary analysis, and the light grey area represents the 95% credible intervals. Odds ratios adjusted for factors listed in statistical analysis.

[c]The posterior probability is the probability that a single day decrease of symptoms was associated with increased progression to organ support and mortality.

[d]High d-dimer was defined as ≥2 times the upper limit of normal. Low dimer was defined as <2 times the upper limit of normal. Upper limit of normal was defined according to local laboratory criteria.

Secondary Outcomes

A single day decrease in symptom duration was associated with a high probability of respiratory support, intubation, increased hospital length of stay, organ support and mortality, mortality, and the composite of thrombosis and mortality (see Figure 4.2.3).

Few patients experienced bleeding events (1.5%, n=17) or thrombotic event (1.4%, n=16) which precluded interpretation of the impact of symptom duration on these outcomes (see Supplementary Appendix Table 4.S.3 and 4.S.4).

Objective #2

In the model without the interaction between treatment arm and symptom duration, therapeutic-dose heparin likely reduced progression to ICU-level organ support and mortality (adjusted OR 1.33, 95% CrI 0.98-1.79, Pr 96.7%) compared to usual care venous thromboprophylaxis. With the interaction included, the treatment effect of therapeutic-dose heparin was unlikely to have varied by symptom duration (Pr of a statistical interaction between treatment arm and symptom duration 27.2%) (see Supplementary Appendix Table 4.S.5 and Figure 4.S.8). This finding was consistent when symptom duration was analyzed categorically or as quartiles (see Supplementary Appendix Figure 4.S.9).

Discussion

In this secondary analysis of a large international randomized trial of adult patients hospitalized for COVID-19, we found that shorter symptom duration prior to hospitalization was associated with increased progression to ICU-level organ support, mortality, and adverse clinical outcomes. While shorter symptom duration appeared to be a consistent marker of disease progression, the treatment effect of heparin did not appear to vary across a range of symptom durations.

In our study we found patient baseline characteristics varied markedly between those with shorter versus longer duration of COVID-19 symptoms. Compared to patients with longer symptom duration, patients with shorter symptom duration were more often female, Black or African American, and from Canada or the United States. Prior studies have not evaluated individual patient characteristics in relation to symptom duration in COVID-19. Social norms, stigma, healthcare resources, and geography are possible factors that may have influenced the observed differences in demographics. Further, patients with shorter symptom duration tended to have more thrombocytopenia and obesity. Severe COVID-19 is associated with higher rates of thrombocytopenia and may explain the observed lower platelet counts in patients with shorter symptom duration as they were more likely to progress to severe disease[88]. Additionally, obesity is a risk factor for severe COVID-19, so it is not surprising that obesity was more common in patients with shorter symptom durations[89].

Symptom duration had a reduced effect on progression to organ support and mortality in patients that were older, had cardiovascular disease, were not on glucocorticoids at baseline, and to a lesser extent in patients that identified as not Hispanic or Latinx, with high d-dimer, and with lower body weights. Why shorter or longer symptom duration affected progression to organ support and mortality in some patients but not others is unclear as this effect was observed across demographics, comorbidities, and laboratory values and did not follow discernable patterns.

Despite clear differences in patient characteristics among those with shorter versus longer symptom durations, we found that treatment with therapeutic-dose heparin appeared unaffected by

symptom duration. The RAPID trial observed a non-statistically significant but potentially clinically relevant reduction in death and mechanical ventilation in the treatment effect of therapeutic-dose heparin for patients with >7 days of symptoms compared to ≤7 days[67]. The FREEDOM and HEP-COVID trials demonstrated that therapeutic-dose heparin reduced mortality, thrombosis, and need for organ support but did not Kingdom indicated that longer symptom duration was strongly associated with worse outcomes [72,73]. A study on H1N1 in Mexico reported a similar effect that delayed hospitalization was associated with increased mortality early (April to July 2009) in the pandemic[74]. A study in Spain evaluating patients between February and May 2020, found that every additional day of symptom prior to hospitalization was associated with decreased mortality[90]. Our study began after the initial phase of the pandemic, took place over a longer time period, and took place in multiple countries which may explain observed differences between the aforementioned studies and ours. Additionally, evolving circumstances surrounding COVID-19 may alter the characteristics and effects of symptom duration that we observed. Vaccinated patients reported longer durations from symptom onset to death and the omicron variant was reported to have a shorter average illness duration compared to the delta variant[91,92].

This study included a diverse population of patients from 60 sites across North and South America. It is the first study to comprehensively evaluate the effect of symptom duration in COVID-19 patients in a clinical trial. Other studies evaluating symptom duration have used administrative and clinical databases which likely have lower data validity than the highly scrutinized data of clinical trials. The large sample size and quantity of data recorded for each patient allowed us to adjust our model for a wide range of patient factors that may not have been readily available in retrospective studies.

There were several limitations associated with the assessment of symptom duration. The date of symptom onset is subject to patient recall bias. In Figure 4.2.2, 1 week and 10 days of symptoms were more common than surrounding days likely due to rounding. There also may be interpatient variability in how individuals defined the severity threshold for what they consider a symptom. Different symptoms have been reported to be associated with varying durations of illness and risks of hospitalization, however ATTACC did not record type of symptom with the date of symptom onset[93,94]. Despite the above limitations, symptom duration was strongly associated with a number of outcomes which supports the generalizability of the measure used in this study.

Conclusion

Shorter symptom duration prior to hospital admission was associated with progression to organ support and mortality in noncritically ill patients hospitalized for COVID-19 and may be used to identify those at risk of disease progression. While therapeutic-dose heparin likely reduced disease progression, patients with shorter or longer symptom duration did not appear to be differentially affected by this treatment.

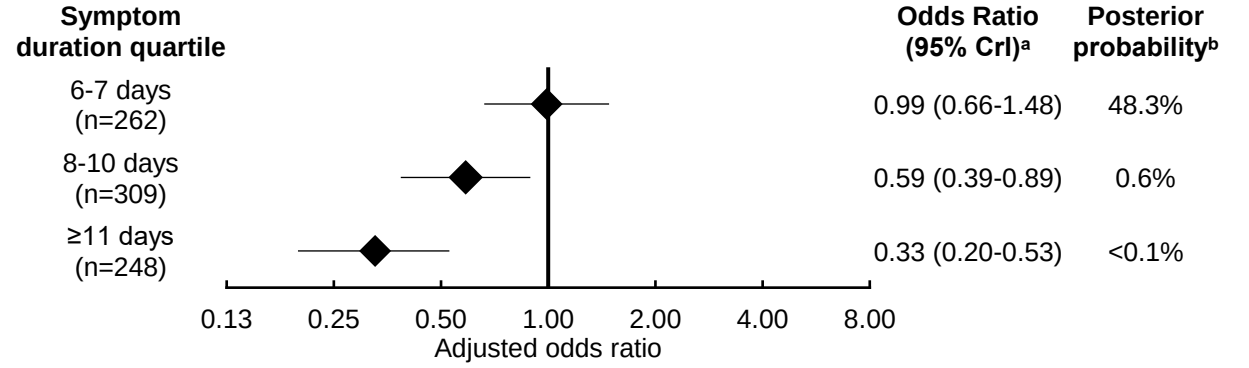
4.S Supplementary Materials & Discussion

This section elaborates on the analysis evaluating symptom and includes materials referenced in the manuscript and discusses them in further detail. Tables and figures are ordered in which they were referenced in the manuscript.

It is possible that the linear effect of symptom duration measured in the primary analysis is not consistent for patients with shorter or longer symptom durations. In the analysis using symptom duration quartiles, the effect of symptom duration was similar to the primary analysis as longer symptom duration quartiles were associated with improved survival without organ support relative to the first symptom duration quartile (0-5 days) (Figure 4.S.1). However, the second quartile (5-6 days) appeared to have a similar effect on survival without organ support as the first quartile which suggests that there may be a threshold up to which the duration of symptoms has little difference how it affects survival without organ support. As the COVID-19 symptom durations for different SARS-CoV-2 variants have been reported to vary, the results of Figure 4.S.1 likely only apply to the timeframe that the study took place[91].

The choice to perform this analysis using quartiles (as opposed to tertiles, quintiles, etc.) was arbitrary. This resulted in quartiles of varying symptom duration lengths with first quartile encompassing 6 days and the second quartile only encompassing 2 days. These quartile bins are not clinically useful therefore it may be better to choose bin number and sizes after determining the distribution of symptom duration in future studies as opposed to choosing quartiles a priori.

Figure 4.S.1: The effect of symptom duration quartile on organ support and mortality[a]



Abbreviations: CrI = credible interval

[a]Odds ratios represent the effect of respective symptom duration quartiles on organ support and mortality relative to the first quartile (0-5 days, n=318). Odds ratios adjusted for factors listed in statistical analysis.

[b]The posterior probability is the probability that a symptom duration quartile was associated with increased progression to organ support and mortality relative to the first symptom duration quartile.

As this study was performed using clinical trial data in which a treatment was applied and was demonstrated to benefit patients, the time between hospital admission and randomization when patients were not receiving said treatment could have been important with regards to disease progression. Additionally, another marker of disease progression, the date of first positive SARS-CoV-2 test may also help identify patients at greater risk of disease progression. As such, several variations of

symptom duration using symptom onset date, date of first positive SARS-CoV-2 PCR test, date of hospital admission, and date of randomization were used in sensitivity analyses (see Table 4.1.2) for descriptions of each analysis). Analyses that used the date of first positive SARS-CoV-2 PCR test included patients from the ACTIV-4a database.

The median time from date of first positive SARS-CoV-2 PCR test and hospital admission (median 1, IQR 0-5) was 6 days shorter than symptom duration prior to hospital admission (median 7, IQR 5-10 (Table 4.S.1 and Figure 4.S.2). This is likely because 44% (817/1834) of patients had their first positive PCR test once they were hospitalized whereby the time difference to hospital admission would be ≤0 days. When PCR test date was used to impute missing symptom duration values, the median duration was 6 days (IQR 1-9) (Figure 4.S.3). The average time between symptom onset and randomization was 1.6 days longer than symptom duration prior to hospital admission which is expected as patients were enrolled within 72 hours after hospital admission (Figure 4.S.4). The distributions of symptom duration prior to hospital admission and symptom duration prior to randomization appeared normal and evenly distributed around the mean and median. The distribution of time between date of first positive SARS-CoV-2 PCR test and hospital admission was skewed to the left of the mean likely due to the number of patients that test positive on the date of hospital admission (n=691).

Despite differences between the variations of symptom duration and the primary analysis, the model effects were remarkably similar as all had >99.9% probability that a single day decrease was associated with increased progression to organ support and mortality (Figure 4.2.5).

Table 4.S.1 Mean and median (IQR) for variations of symptom duration in primary and sensitivity analyses

Starting date	Ending date	Mean difference (days)	Median difference (IQR) (days)
Symptom onset	Hospitalization[a]	8.1	7 (5-10)
First positive PCR test	Hospitalization[b]	3.1	1 (0-5)
Symptom onset or first positive PCR test	Hospitalization[c]	6.4	6 (1-9)
Symptom onset	Randomization[d]	9.7	9 (7-12)

Abbreviations: IQR = interquartile range, PCR = polymerase chain reaction

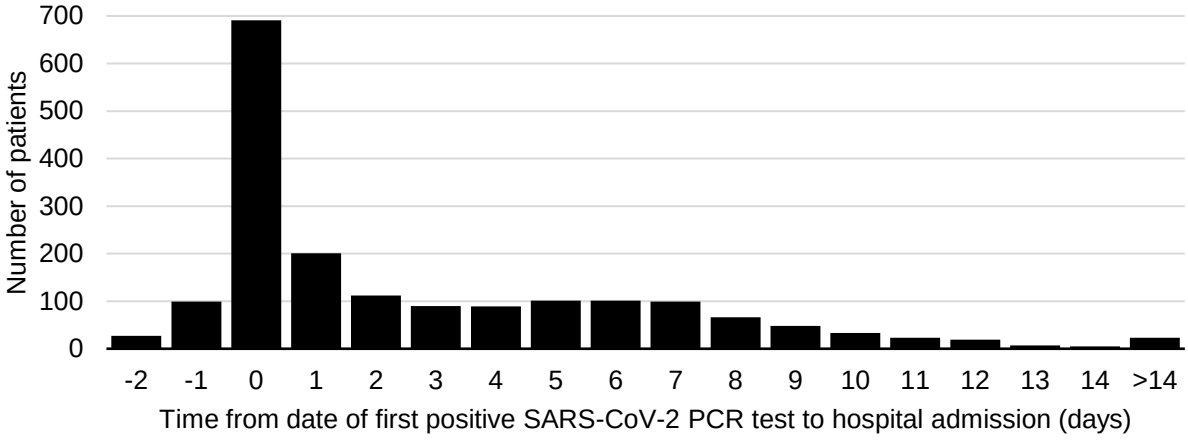
[a]Analysis of symptom onset to hospitalization was the primary analysis.

[b]Analysis with first positive PCR test to hospitalization used the difference between date of first positive SARS-CoV-2 PCR test and date of hospitalization as the main predictor variable. [e]This analysis used both the ATTACC and ACTIV-4a data sets.

[c]Analysis with symptom onset or first positive PCR test to hospitalization used the difference between symptom onset and hospitalization when available. For patients with no symptom onset but had a date of first positive SARS-CoV-2 PCR test, symptom duration was obtained by taking the difference between first positive SARS-CoV-2 PCR test and hospitalization. Patients with negative symptom duration values were excluded. This analysis used both the ATTACC and ACTIV-4a data sets.

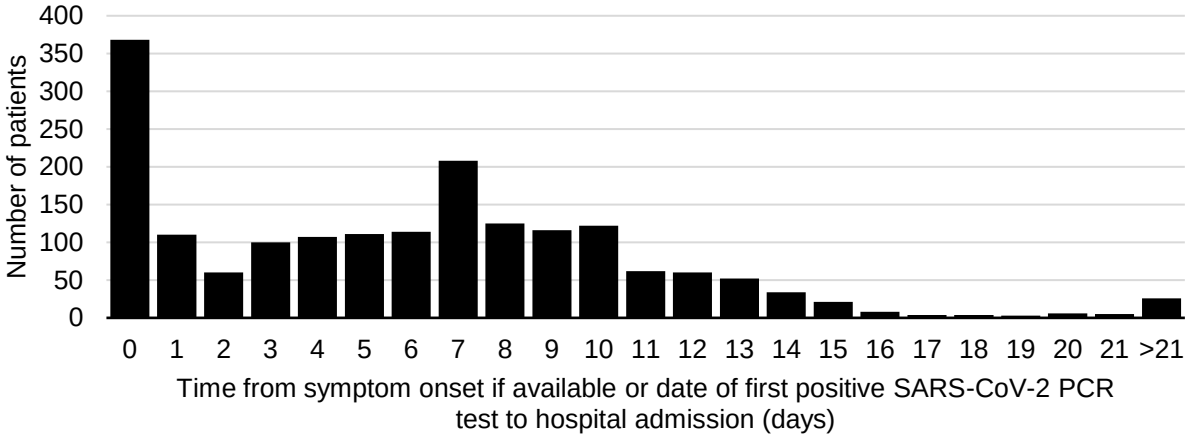
[d]Analysis with symptom onset to randomization used the difference between date of symptom onset and date of randomization into the trial as the main predictor variable. This analysis only used the ATTACC data set.

Figure 4.S.2: Distribution of time from first positive SARS-CoV-2 PCR test to hospital admission



Abbreviations: PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Figure 4.S.3: Distribution of time from symptom onset if available or date of first positive SARS-CoV-2 PCR test to hospital admission



Abbreviations: PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Figure 4.S.4: Distribution of time from symptom onset to randomization

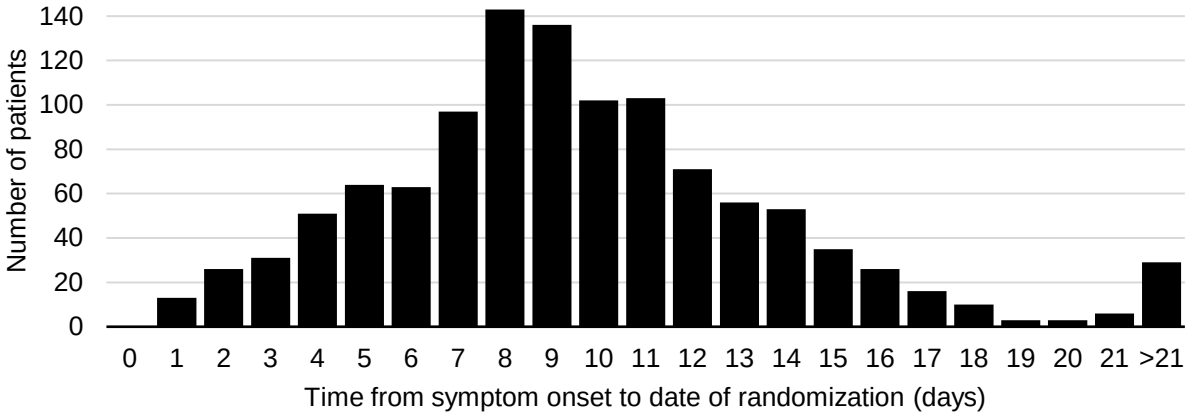
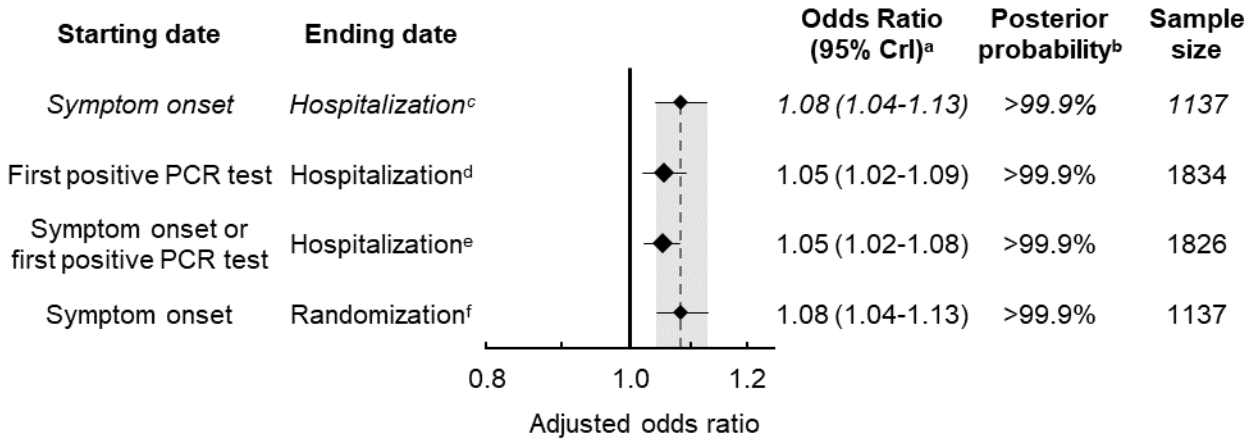


Figure 4.S.5: The effect a single day decrease in variations of symptom duration on organ support and mortality

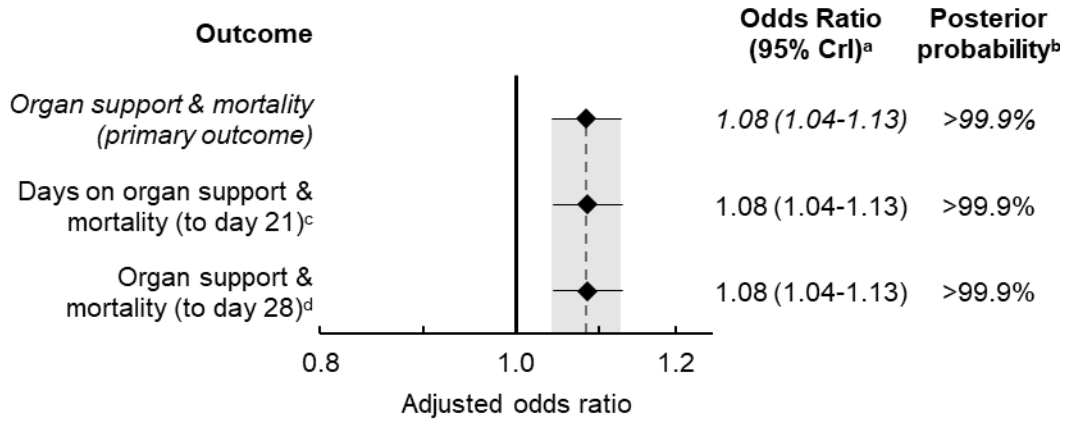


Abbreviations: CrI = credible interval.
[a]Odds ratios represent the effect of a single day decrease of a given symptom duration variant (difference between the starting date and ending date) on survival without organ support. Odds ratios adjusted for factors listed in statistical analysis.
[b]The posterior probability is the probability that a single day decrease in a given symptom duration variant was associated with increased progression to organ support and mortality.
[c]Analysis of symptom onset to hospitalization was the primary analysis.
[d]Analysis with first positive PCR test to hospitalization used the difference between date of first positive SARS-CoV-2 PCR test and date of hospitalization as the main predictor variable. [e]This analysis used both the ATTACC and ACTIV-4a data sets.
[e]Analysis with symptom onset or first positive PCR test to hospitalization used the difference between symptom onset and hospitalization when available. For patients with no symptom onset but had a date of first positive SARS-CoV-2 PCR test, symptom duration was obtained by taking the difference between first positive SARS-CoV-2 PCR test and hospitalization. Patients with negative symptom duration values were excluded. This analysis used both the ATTACC and ACTIV-4a data sets.
[f]Analysis with symptom onset to randomization used the difference between date of symptom onset and date of randomization into the trial as the main predictor variable. This analysis only used the ATTACC data set.

Given that previous publications on this data had used a composite of organ support-free days and mortality as the primary outcome, to evaluate the appropriateness of the primary outcome two ordinal variations of the primary outcome were used in sensitivity analyses (Figure 4.S.6)[10,66]. Results

were so similar that they only varied at greater than 2 decimal places of the odds ratios and 95% credible intervals. Additionally, the secondary outcome of "survival without organ support (to day 28)" which was a binary outcome also displayed identical results up to 2 decimal places (Figure 4.2.3). Therefore, there are several feasible methods to evaluate survival without organ support with respect to symptom duration.

Figure 4.S.6: The effect of shorter symptom duration on variations of progressions to organ support and mortality



Abbreviations: CrI = credible interval.
[a]Odds ratios represent the effect of a single day decrease in symptoms for each respective outcome. Odds ratios vary past 2 decimal places. Given the similarity of the odds ratios and credible intervals, these models were double checked. Odds ratios adjusted for factors listed in statistical analysis.
[b]The posterior probability is the probability that a single day decrease of symptoms was associated with increased progression to a given outcome.
[c]Days on organ support and mortality was defined as an ordinal measure of number of days receiving ICU-level organ support up to day 21 (0-21). Patients that didn't receive organ support up to day 21 were designated 22. Patients that died in hospital by day 90 were designated -1. Patients discharged prior to day 21 were treated as alive and not having received organ support post-discharge. This outcome was referred to in previous publication on this data as "organ support-free days".
[d]Organ support and mortality (to day 28) was defined as an ordered categorical endpoint with three possible outcomes based on the worst status of each patient to day 28 following randomization: 1) Survived through index hospitalization or up to day 28, never on organ support up to day 28; 2) Survived through index hospitalization or up to day 28, received organ support up to day 28; 3) Died during index hospitalization through day 28.

To evaluate the effects symptom duration on survival without organ support for different patient characteristics, several subgroup analyses were performed (Figure 4.2.4). There were distinct differences in the effect of symptom duration by age group. Age was analyzed post hoc with an interaction variable between age and symptom duration (age*symptom duration) (Table 4.S.2). There was >99.9% probability that an additional year reduced (equivalent to <0.1% probability of superiority reported in Table 4.S.2) the effect of symptom duration on survival without organ support. This interaction was also analyzed using age categories which demonstrated that patients older than 70 were less affected by symptom duration (Figure 4.S.7). Together, these results indicated that there is a strong interaction between symptom duration and age whereby symptom duration has less of an effect on progression to organ support and mortality in older patients.

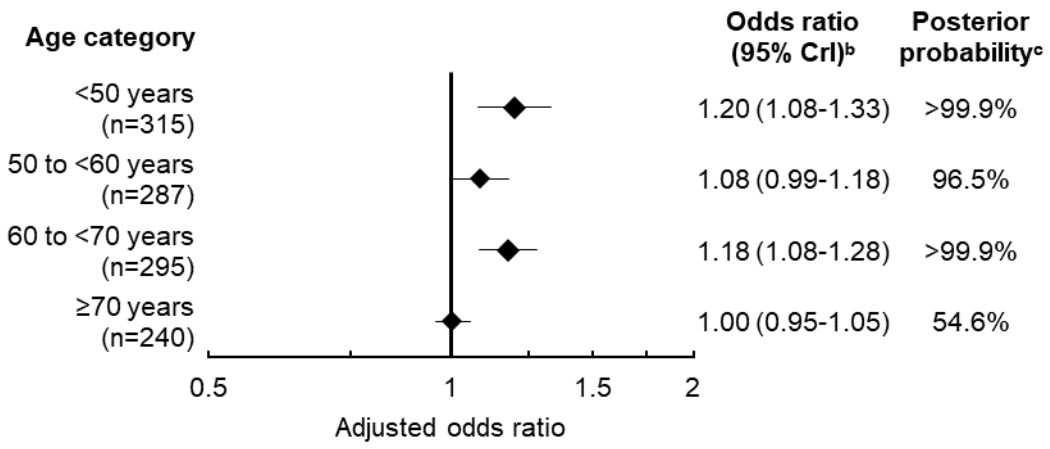
The effect of symptom duration did not appear to vary by sex, baseline antiplatelet, chronic kidney disease, and race. However, Patients with chronic kidney disease and some racial groups were underrepresented.

Table 4.S.2: Interaction between age and symptom duration

	Odds Ratio (95% CrI)[a]	Posterior probability[b]
Symptom duration (at age = 0 years)	1.49 (1.27-1.74)	>99.9%
Age (at symptom duration = 0 days)	1.003 (0.983-1.022)	60.80%
Interaction (symptom duration*age)	0.995 (0.993-0.997)	<0.1%

[a]The odds ratio for symptom duration represents the effect of a single day decrease in symptoms on progression to organ support and mortality. The odds ratio for age represents the effect of an additional year of age on progression to organ support and mortality. The odds ratio for the interaction variable represents the rate of change of an additional year of age on the effect of a single day decrease of symptoms on progression to organ support and mortality.
[b]For symptom duration, the posterior probability is the probability that a single day decrease of symptoms was associated with increased progression to organ support and mortality. For age, it is the probability that a 1-year increase in age reduced progression to organ support and mortality. For the interaction variable, it is the probability that an additional year of age increased the effect of symptom duration on organ support and mortality.

Figure 4.S.7: The effect of shorter symptom duration on organ support and mortality by age group[a]



Abbreviations: CrI = credible interval
[a]This model included an interaction variable between symptom duration and age category.
[b]Odds ratios represent the effects of a single day decrease in symptoms on progression to organ support and mortality. Odds ratios adjusted for factors listed in statistical analysis.
[c]The posterior probability is the probability that a single day decrease of symptoms was associated with increased progression to organ support and mortality.

Bleeding was relatively rare with a total incidence of 1.5% (17/1137) (Table 4.S.3). Bleeding events were more common in patients that were assigned to therapeutic-dose heparin (1.9%, 12/638)

compared with usual care venous thromboprophylaxis (1.0%, 5/499). Bleeding events did not appear to vary by symptom duration quartiles which is consistent with analysis of major bleeding (Figure 4.2.3).

Table 4.S.3: ISTH major bleeding events[a]

Category		Intervention	Symptom duration quartile			
			0-5 days (n=318)	**6-7 days (n=262)**	**8-10 days (n=309)**	**≥11 days (n=248)**
Number of patients with a bleeding event/total Percent (95% CrI)		Therapeutic-dose heparin	2/177 1.1% (0.3-4.0)	5/150 3.3% (1.5-7.6)	3/170 1.8% (0.6-5.0)	2/141 1.4% (0.4-5.0)
		Usual care venous thromboprophylaxis	3/141 2.1% (0.8-6.0)	0/112 0% (0.0-3.2)	0/139 0% (0.0-2.6)	2/107 1.9% (0.6-6.5)
Bleeding event breakdown						
Number of events	Overt bleeding causing a fall in hemoglobin ≥ 2 g/dL or leading to transfusion of ≥ 2 units of whole blood or red cells	Therapeutic-dose heparin	3	6	4	3
		Usual care venous thromboprophylaxis	5	0	0	4
	Overt and symptomatic bleeding in a critical area or organ[b]	Therapeutic-dose heparin	2	2	1	1
		Usual care venous thromboprophylaxis	1	0	0	0
	Fatal bleeding	Therapeutic-dose heparin	0	0	1	0
		Usual care venous thromboprophylaxis	1	0	0	0

Abbreviations: CrI = credible interval, LMWH = low molecular weight heparin, UFH = unfractionated heparin.
[a]Includes all major bleeding events up to 90 days post randomization. Bleeding events were adjudicated in a blinded fashion by a separate committee using criteria from the International Society on Thrombosis and Haemostasis for major bleeding in non-surgical patients (see Appendix section 8.4). Bleeding event criteria were not mutually exclusive.
[b]Under "overt and symptomatic bleeding in a critical area or organ" only retroperitoneal bleeding was observed.

Thrombosis was likewise uncommon with a total incidence of 1.4% (16/1137). Patients assigned to therapeutic-dose heparin had slightly lower incidence of thrombotic events (1.3%, 8/638) than patients assigned to usual care venous thromboprophylaxis (1.6%, 8/499) (Table 4.S.4). There were more patients with thrombotic events with symptom durations ≤7 days (1.7%, 10/580) than patients with symptom duration >7 days (1.1%, 6/547). This is consistent with the result that shorter symptom duration was associated with an increased composite of thrombosis and mortality (Figure 4.2.3).

Table 4.S.4: Thrombotic events during index hospitalization[a]

Category		Intervention	Symptom duration quartile			
			0-5 days (n=318)	6-7 days (n=262)	8-10 days (n=309)	≥11 days (n=248)
Number of patients with an in-hospital thrombotic event Percent (95% CrI)		Therapeutic-dose heparin	3/177 1.7% (0.6-4.8)	3/150 2.0% (0.7-5.7)	0/170 0% (0.01-2.1)	2/141 1.4% (0.4-5.0)
		Usual care venous thromboprophylaxis	3/141 2.1% (0.8-6.0)	1/112 0.9% (0.2-4.8)	1/139 0.7% (0.2-3.9)	3/107 2.8% (1.0-7.9)
Thrombotic event breakdown						
Number of events	All thrombotic events	Therapeutic-dose heparin	4	5	0	2
		Usual care venous thromboprophylaxis	3	1	1	3
	All venous thromboembolic events	Therapeutic-dose heparin	2	5	0	2
		Usual care venous thromboprophylaxis	2	1	1	2
	Pulmonary embolism	Therapeutic-dose heparin	1	3	0	0
		Usual care venous thromboprophylaxis	1	1	0	2
	Deep vein thrombosis	Therapeutic-dose heparin	1	2	0	2
		Usual care venous thromboprophylaxis	1	0	1	0
	All arterial events	Therapeutic-dose heparin	2	0	0	0
		Usual care venous thromboprophylaxis	1	0	0	1
	Myocardial infarction	Therapeutic-dose heparin	0	0	0	0
		Usual care venous thromboprophylaxis	1	0	0	0
	Ischemic cerebrovascular event	Therapeutic-dose heparin	0	0	0	0
		Usual care venous thromboprophylaxis	0	0	0	0
	Systemic arterial thromboembolism	Therapeutic-dose heparin	2	0	0	0
		Usual care venous thromboprophylaxis	0	0	0	1

Abbreviations: CrI = credible interval, LMWH = low molecular weight heparin, UFH = unfractionated heparin.
[a]Includes all thrombotic events that occurred in hospital up to day 90. Thrombotic events were adjudicated in a blinded fashion by separate committees using consensus criteria (see Appendix section 8.3). Thrombotic events were not mutually exclusive.

The results of the model that analyzed the interaction between the treatment effect of heparin and symptom duration (continuous) are depicted visually as point estimates for symptom durations from 0-15 days (Table 4.S.5 and Figure 4.S.8). While the point estimates for the odds ratio change with increasing symptom duration which would be expected with any non-zero odds ratio of the interaction, the credible intervals greatly overlap with one another from the shortest to longest symptom durations. Together, this overlap and the posterior probability of the interaction variable (Pr, 27.2%) indicate that it

was unlikely that there was variation in the treatment effect of heparin by symptom duration. This is supported by the analysis of the interaction between treatment arm and symptom duration quartiles which also demonstrate great overlap of the credible intervals of the treatment effect of therapeutic-dose heparin by symptom duration quartile (Figure 4.S.9).

Table 4.S.5: Interaction between symptom duration (continuous) and randomized treatment group

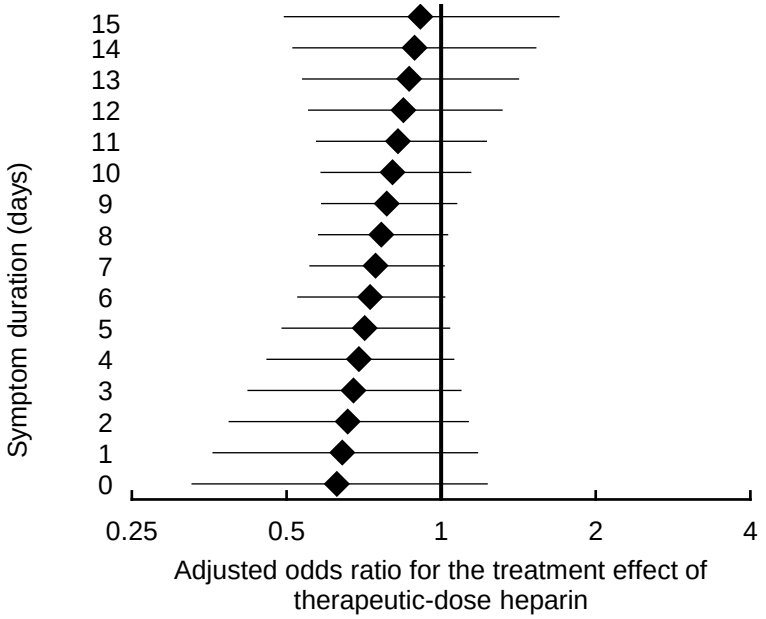
Model effect	Odds Ratio (95% CrI)[a]	Posterior Probability[b]
Symptom duration (for usual care venous thromboprophylaxis)	1.10 (1.03-1.17)	>99.9%
Treatment group (at symptom duration = 0 days)	0.63 (0.33-1.20)	Benefit: 91.9% Harm: 8.1%
Interaction (symptom duration*treatment group)	1.02 (0.95-1.11)	72.8%

Abbreviations: CrI = credible interval.

[a]The odds ratio for symptom duration represents the effects of a single day decrease in symptoms on progression to organ support and mortality. The odds ratio for treatment arm represents the effect of therapeutic-dose heparin on progression to organ support and mortality compared to usual care venous thromboprophylaxis. The odds ratio for the interaction variable represents the rate of change of the treatment effect of therapeutic-dose heparin compared to usual care venous thromboprophylaxis for a single day decrease of symptoms on progression to organ support and mortality.

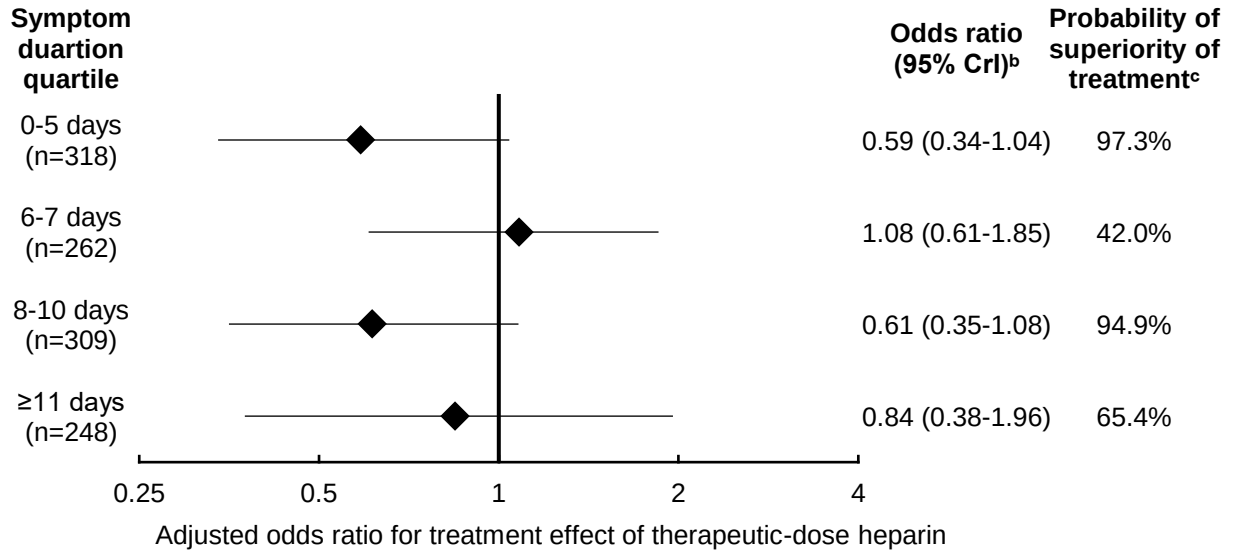
[b]For symptom duration, the posterior probability is the probability that a single day decrease of symptoms was associated with increased progression to organ support and mortality. For treatment group, it is the probability that therapeutic-dose heparin reduced progression to organ support and mortality compared to usual care venous thromboprophylaxis. For the interaction variable, it is the probability that a single day decrease in symptoms increased the effect of therapeutic-dose heparin on progression to organ support and mortality compared to usual care venous thromboprophylaxis.

Figure 4.S.8: The effect of therapeutic-dose heparin on progression to organ support and mortality by symptom duration[a]



[a]Odds ratios represent the treatment effect of therapeutic-dose heparin relative to usual care venous thromboprophylaxis on progression to organ support and mortality for a given symptom duration. Odds ratios adjusted for factors listed in statistical analysis.

Figure 4.S.9: The effect of therapeutic-dose heparin on progression to organ support and mortality by symptom duration quartile[a]



Abbreviations: CrI = credible interval

[a]This model included an interaction variable between treatment arm and each symptom duration quartile.

[b]Odds ratios represent the effect of therapeutic-dose heparin relative to usual care venous thromboprophylaxis for a given symptom duration quartile on progression to organ support and mortality. Odds ratios adjusted for factors listed in statistical analysis.

[c]The probability of superiority of treatment is the probability that therapeutic-dose heparin reduced progression to organ support and mortality for patients relative to usual care venous thromboprophylaxis.

5. Conclusions

In the analysis of **heparin type**, enoxaparin was the most commonly used type of heparin in both treatment groups. Baseline characteristics between patients that were assigned to usual care venous thromboprophylaxis, were administered therapeutic-dose LMWH, and were administered therapeutic-dose UFH were similar, however, those that were administered UFH had more comorbidities and lower eGFRs. Model inferences for patients in the therapeutic-dose arm that were administered dalteparin, other LMWHs, and UFH were limited due to their relatively small sample sizes. Therapeutic-dose enoxaparin likely improved survival without organ support compared to usual care venous thromboprophylaxis. Therapeutic-dose enoxaparin also likely reduced a composite of thrombosis and mortality but at the cost of a small increase in bleeding risk.

In the analysis of **symptom duration**, patients with shorter symptom duration prior to hospital admission were more likely to identify as female, Black or African American, had more comorbidities, had lower platelet counts, be enrolled in Canada or the US, weighed more, and had higher body mass indices. Shorter symptom duration strongly was associated with increased progression to organ support and mortality, respiratory support respiratory support and mortality, intubation, days hospitalized, organ support and mortality at 28 days, and the composite of thrombosis and mortality. Symptom duration can aid clinicians in identifying patients that are likely to progress to more severe disease. The effect of symptom duration on progression to organ support and mortality more pronounced in younger patients, those without cardiovascular disease, and those on glucocorticoids at baseline.

It was unlikely that the treatment effect of therapeutic-dose heparin compared to usual care venous thromboprophylaxis varied across a range of symptom durations.

6. Future Research

Our study was unable to discern the treatment effects of non-enoxaparin heparins due to small sample sizes. It is likely that other LMWHs have a similar treatment effect to enoxaparin's due to similarity in molecular properties, but this still needs to be further evaluated using clinical data. Given UFH has very distinct properties from LMWHs and may behave differently in the treatment of noncritically ill patients with COVID-19 and should also be evaluated in future studies separate from LMWHs.

Therapeutic-dose heparin was harmful for *critically* ill patients[66,69]. Again, there may be differences in the treatment effect of heparin by type, particularly between LMWHs and UFH. The third platform of this trial was REMAP-CAP which was not included in our study as it focused primarily on critically ill patients. A future study can use the framework from our study on the REMAP-CAP database to evaluate the treatment effect of different heparins for patients that start therapeutic-dose heparin in the ICU.

For symptom duration, our model used a logistic regression that didn't include factors of time, other than symptom duration itself. A time-to-event model may be useful in analyzing other facets of disease progression such as time to ICU admission. Symptom duration may be proportional to the time from hospital admission to ICU admission or even may represent the "velocity" of disease progression given the strong association with disease progression that we observed.

As our study did not record type of COVID-19 symptom. Future studies could evaluate the risk of disease progression for different types of symptoms. A study on outpatient healthcare workers with COVID-19 found that shortness of breath, fever, sore throat, and diarrhea was associated with longer illness duration[94]. Its possible that these symptoms, and others, may be associated with disease severity in hospitalized patients as well.

Given that early reports of symptom duration found that longer symptom duration prior to hospital admission was associated with poor clinical outcomes, it may be apt to adjust for healthcare resource availability[72,73]. There were several points in the pandemic when ICUs were at or over their normal capacities as they would have been during the early reports of symptom duration. Evaluating symptom duration during these fluctuations may demonstrate how symptom duration behaves according to healthcare resource availability.

We are entering an endemic phase of COVID-19 where there are fewer cases of COVID-19. Patients may have different characteristics which could result in a different average symptom duration with a different relationship to disease progression. The results of our study could be validated using observational or administrative data sets.

Different variants of the SARS-CoV-2 were associated with different average symptom durations prior to hospital admission[91]. Our study did not record SARS-CoV-2 variants and therefore describes the symptom duration of the averages of multiple variants. Some variants may have greater risk of disease progression with regards to symptom duration and it would be useful for clinicians to know if one variant is associated with higher risk of progression with regards to symptom duration.

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8. Appendix

8.1 Heparin Type Adjudication

Heparin type was adjudicated using anticoagulant records on day 1 (day after randomization). For cases that had multiple types of heparins administered on day 1, the type of heparin with the higher dose category was used (see Appendix 8.2.1 for dose adjudication rules). There were no cases in which multiple types had the same dose category.

Additional Heparin Type Adjudication Notes

- There were 107 patients with no record of heparin on day 1.
- There were 18 patients that had records of receiving multiple types of heparins on day 1.
    - All these cases involved the use of UFH and one type of LMWH.
- Dalteparin was only used in Canada.
- Bemiparin was only used at one site in Spain (ES-2005).
- Patients with “other, please specify” for their day 1 heparin type were mostly listed as “heparin” or “heparin (porcine) injection”. Most of these cases were identified as being UFH based on their schedule and route of administration.
- For patients receiving a continuous infusion (only UFH was continuous), time of start/end was included to make a more accurate estimation of dose received in the day (i.e., a record starting an infusion of 1000 IU/hour starting at noon and continuing into the next will be multiplied by 12 hours to get the total dose).
    - For records without time available (i.e., data granularity only to the level of calendar date), calculations were done based on 24 hours (i.e. record with 1000 IU/hour with no specified time would be assumed to be 1000*24 = 24000 IU).
        - For a patient with 'n' records on day 1, each record would have an assigned time of 24/n hours (e.g., a patient with 3 separate records of heparin on a single day would assign 8 hours to each).
- One patient had “tablet” listed as units for enoxaparin which was treated as mg.

8.2 Heparin Dose adjudication

The guidelines used to adjudicate dose categories are listed below in Tables 8.1.1-8.1.5 are adapted from Table 3 of American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19[95].

Table 8.2.1 ASH guidelines for enoxaparin dose categories

	Heparin regimen	Low-dose	Intermediate-dose	Sub-therapeutic-dose	therapeutic-dose
	OD	40 mg	Up to 1.2 mg/kg	-	Lower limit 1.35 mg/kg

BMI <40 kg/m^2 & CrCl ≥30 mL/min	*BID*	Not defined	*Up to 1.2 mg/kg or 40 mg (twice) whichever is higher*	-	Lower limit 1.8 mg/kg
BMI ≥40 kg/m^2 or weight >120 kg & CrCl ≥30 mL/min	*OD*	Not defined	Up to 0.96 mg/kg	Not defined	Not defined
	BID	80 mg	Up to 120 mg	-	Lower limit 1.44 mg/kg
CrCl <30 mL/min	*OD*	30 mg	Up to 0.6 mg/kg	-	Lower limit 0.9 mg/kg
	BID	Not defined	Not defined	Not Defined	Not defined

Abbreviations: BMI = body mass index, CrCl = creatinine clearance, OD = once daily, BID = twice daily
Footnotes: All adjudication categories refer to subcutaneously administered heparin. Values refer to the total daily dose received. The lower limits for therapeutic-doses by body weight are reduced by 10% from the American Society of Hematology guidelines. Patients that received one type of heparin >2 times in day were adjudicated with the twice daily schedule for heparin administration. Doses between low- and intermediate-dose were assigned to intermediate-dose. In cases where intermediate and therapeutic-dose limits are defined, sub-therapeutic doses occur between these definitions. Doses of 40 mg OD without weight/BMI were always assigned low-dose. Dose of 60 IU OD for patients with BMI >40 kg/m2 and CrCl ≥30 mL/min were assigned low-dose.

Table 8.1.2 ASH guidelines for dalteparin dose categories

	Heparin regimen	**Low-dose**	**Intermediate-dose**	**Sub-therapeutic-dose**	**therapeutic-dose**
BMI <40 kg/m^2 & CrCl ≥30 mL/min	*OD*	5000 IU	Not defined	Not defined	135 IU/kg
	BID	Not defined	10000 IU	-	180 IU/kg
BMI ≥40 kg/m^2 or weight >120 kg & CrCl ≥30 mL/min	*OD*	7500 IU	Not defined	Not defined	Not defined
	BID	Not defined	15000 IU	Not defined	Not defined
CrCl <30 mL/min	*OD*	Not defined	Not defined	Not defined	Not defined
	BID	Not defined	Not defined	Not defined	Not defined

Abbreviations: BMI = body mass index, CrCl = creatinine clearance, OD = once daily, BID = twice daily
Footnotes: All adjudication categories refer to subcutaneously administered heparin. Values refer to the total daily dose received. The lower limits for therapeutic-doses by body weight are reduced by 10% from the American Society of Hematology guidelines. Patients that received one type of heparin >2 times in day were adjudicated with the twice daily schedule for heparin administration. Doses between low- and intermediate-dose were assigned to intermediate-dose. In cases where intermediate and therapeutic-dose limits are defined, sub-therapeutic doses occur between these definitions. Doses of 5000 IU OD without weight/BMI were always assigned low-dose.

Table 8.1.3 ASH guidelines for tinzaparin dose categories

	Heparin regimen	Low-dose	Intermediate-dose	Sub-therapeutic-dose	therapeutic-dose
BM I<40 kg/m^2 & CrCl ≥30 mL/min	*OD*	Up to 4500 IU or 75 anti-Xa units (whichever is higher)	Not defined	Not defined	157.5 IU/kg

	BID	Not defined	9000 IU	Not defined	Not defined
BMI ≥40 kg/m^2 or weight >120 kg & CrCl ≥30 mL/min	*OD*	8000 IU	Not defined	Not defined	Not defined
	BID	Not defined	16000 IU	Not defined	Not defined
CrCl <30 mL/min	*OD*	Not defined	Not defined	Not defined	Not defined
	BID	Not defined	Not defined	Not defined	Not defined

Abbreviations: BID = twice daily, BMI = body mass index, CrCl = creatinine clearance, OD = once daily, IU = international units
Footnotes: All adjudication categories refer to subcutaneously administered heparin. Values refer to the total daily dose received. The lower limits for therapeutic-doses by body weight are reduced by 10% from the American Society of Hematology guidelines.

Table 8.1.4 ASH guidelines for bemiparin dose categories

	Heparin regimen	Low-dose	therapeutic-dose
Weight ≤50 kg & CrCl ≥30 mL/min	OD	3500 IU	5000 IU
Weight 50-70 kg & CrCl ≥30 mL/min	OD	3500 IU	7500 IU
Weight 70-100 kg & CrCl ≥30 mL/min	OD	3500 IU	10000 IU
Weight >100 kg & CrCl ≥30 mL/min	OD	3500 IU	115 IU/kg

Abbreviations: BMI = body mass index, CrCl = creatinine clearance, IU = international units, OD = once daily
Footnotes: All adjudication categories refer to subcutaneously administered heparin. Values refer to the total daily dose received. Patients that received one type of heparin >2 times in day were adjudicated with the twice daily schedule for heparin administration.

Table 8.1.5 ASH guidelines for UFH dose categories

	Heparin regimen	Low-dose	Intermediate-dose	Sub-therapeutic-dose	therapeutic-dose
BMI <40 kg/m^2 & CrCl ≥30 mL/min	TID	15000 IU	22500 IU	Not defined	Not defined
	BID	Not defined	20000 IU	Not defined	Not defined
BMI ≥40 kg/m^2 or weight >120 kg & CrCl ≥30 mL/min	TID	Not defined	Not defined	Not defined	Not defined
	BID	15000 IU	20000 IU	Not defined	Not defined

Abbreviations: BID = twice daily, BMI = body mass index, CrCl = creatinine clearance, IU = international units, TID = thrice daily, UFH = unfractionated heparin.

Footnotes: All adjudication categories refer to subcutaneously administered heparin. Values refer to the total daily dose received. Continuous infusions of UFH were always assigned therapeutic-dose. Doses between low- and intermediate-dose were assigned to intermediate-dose. A total daily dose of >22500 IU was assigned therapeutic-dose. <15000 IU total daily dose was always assigned as low-dose. Doses of 5000 IU TID without weight/BMI were always assigned low-dose. Patients that received a dose of unfractionated heparin >3 times in day were adjudicated with the TID schedule for heparin administration. Cases where the total daily dose was greater than the intermediate dose but was not a continuous dose were assigned to therapeutic-dose.

8.3 Thrombosis definitions

Adapted from the supplementary index of Lawler et. al.[10]

ATTACC

The full list of secondary endpoints is available in the trial protocol. Among these, the following secondary efficacy endpoints will be adjudicated by the clinical endpoint committee (CEC):

- Venous thromboembolism (DVT or PE) assessed at 28- and 90-days following randomization.
- Myocardial infarction assessed at 28- and 90-days following randomization.
- Ischemic stroke assessed at 28and 90days following randomization.

Systemic arterial thrombosis or embolism assessed at 28- and 90-days following randomization.

- The following secondary safety events will be adjudicated by the CEC (sites instructed to report events occurring during the intervention window as defined in the protocol):
- Laboratory confirmed HIT.

Major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients.[96]

ATTACC endpoint definitions are as described below for ACTIV-4a

ACTIV-4a

The full list of secondary endpoints is available in the trial protocol:

- Deep venous thromboembolism
- Pulmonary embolism
- Arterial thromboembolism
- Myocardial infarction
- Stroke
- Major bleeding
- Death due to cardiovascular, non-cardiovascular, and undetermined cause

Deep Venous Thromboembolism

The diagnosis of definite symptomatic deep venous thromboembolism (DVT) requires symptoms of venous thromboembolism with at least one of the following:

- Abnormal compression ultrasound consistent with DVT or abnormal flow pattern or direct clot visualization in veins not amenable to compression.
- One or more new filling defects by venography, CT venography, or MR venography.
- Abnormal compression ultrasound where compression had been normal or, if known to be non-compressible, a substantial increase (≥4mm) in the diameter of a previously non-compressible venous segment.
- Point-of-care ultrasound (POCUS) performed by a provider and documenting DVT in a note.

- An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography. Proximal DVT is defined as clot at or proximal to the trifurcation of the popliteal vein (in the lower extremity) OR clot at or proximal to the axillary vein segment (in the upper extremity).
- Distal DVT is defined as clot distal to the trifurcation of the popliteal vein (in the lower extremities) OR clot at or distal to the brachial vein segment (in the upper extremities).
- Non-limb venous thrombosis includes thrombosis of the cerebral, portal, mesenteric, hepatic, gonadal, splenic, renal, or retinal veins, or thrombosis of the superior or inferior vena cava.

The diagnosis of presumed deep venous thromboembolism requires the following:

- In the absence of objective testing, high pre-test probability according to investigator assessment
    - OR adjudicator's gestalt
    - OR Wells score
- AND a treatment plan for DVT was initiated (initiation of anticoagulation, or escalation of anticoagulation dose, frequency, or duration).

Pulmonary Embolism

The diagnosis of definite pulmonary embolism requires at least one of the following:

- New intraluminal filling defect at CT pulmonary angiography in a subsegmental or larger vessel.
- New intraluminal filling defect, or an extension of an existing defect, or a new sudden cut-off of vessels > 2.5 mm in diameter at pulmonary angiogram,
- Inconclusive CT pulmonary angiography, pulmonary angiography, or V/Q scan evidence of a new or recurrent PE with demonstration of a new or recurrent DVT in the lower extremities by compression ultrasonography or venography.[97,98]
- New clot or intraluminal filling defect noted in the right heart ("clot in transit") or the pulmonary vasculature at echocardiogram.
- High probability (revised PIOPED criteria) on planar ventilation/perfusion (V/Q) scan OR positive PE on SPECT ventilation perfusion (V/Q) scan.
- Pulmonary embolism found at autopsy.

The diagnosis of presumed pulmonary embolism requires the following:
Clinical signs and symptoms of pulmonary embolism, including but not limited to: dyspnea, cough, hypoxemia, tachycardia, appropriate electrocardiographic changes, or evidence of right heart strain on echocardiogram; AND chest CT or pulmonary angiography are unable to be performed AND therapeutic-dose anticoagulation or fibrinolytic therapy is prescribed by a physician

Arterial Thromboembolism

The diagnosis of arterial thromboembolism is defined as the following:

- A clinical history and presentation consistent with a sudden significant worsening of end organ or limb perfusion AND

EITHER

- Confirmation of arterial obstruction by imaging, hemodynamics, intraoperative findings, or pathological evaluation

OR

- Requirement for thrombolysis, thrombectomy, or urgent bypass.

Note that arterial thromboembolism includes both acute in situ thrombotic events and acute embolic events. Note that while ischemic stroke and myocardial infarction can be arterial thromboembolic events, those events will be adjudicated according to the separate standardized criteria included below.

Myocardial Infarction

COVID-19 patients are well known to have elevations in cardiac troponin concentrations, and these elevations often do not represent arterial thrombosis and downstream myocardial ischemia. Therefore, the CEC will make an effort to distinguish true myocardial infarction from coronary artery obstruction, typically from atherothrombosis (usually considered a "type 1 myocardial infarction") from myocardial infarction due to demand ischemia (usually defined as a "type 2 myocardial infarction") and myocardial injury (an elevation in cardiac troponin typically without symptoms of chest pain or signs of arterial thrombosis). These definitions will be consistent with the 4thUniversal Definition of Myocardial Infarction and will take into considerations suggestions made about classification of certain conditions as type 1 as compared to type 2 myocardial infarction.[99,100] Regional coronary venous thrombosis with associated regional myocardial infarction has been reported in COVID. If this mechanism is documented, these will be considered a type 1 MI. The trial and CEC are focused on ascertaining and adjudicating cases of acute myocardial injury and acute myocardial infarction and classifying those cases as described below. COVID also causes microvascular thrombi which are associated with patchy myocardial necrosis. These will be grouped with myocardial injury.

Figure 8.3.1. Model for interpreting myocardial injury [99]

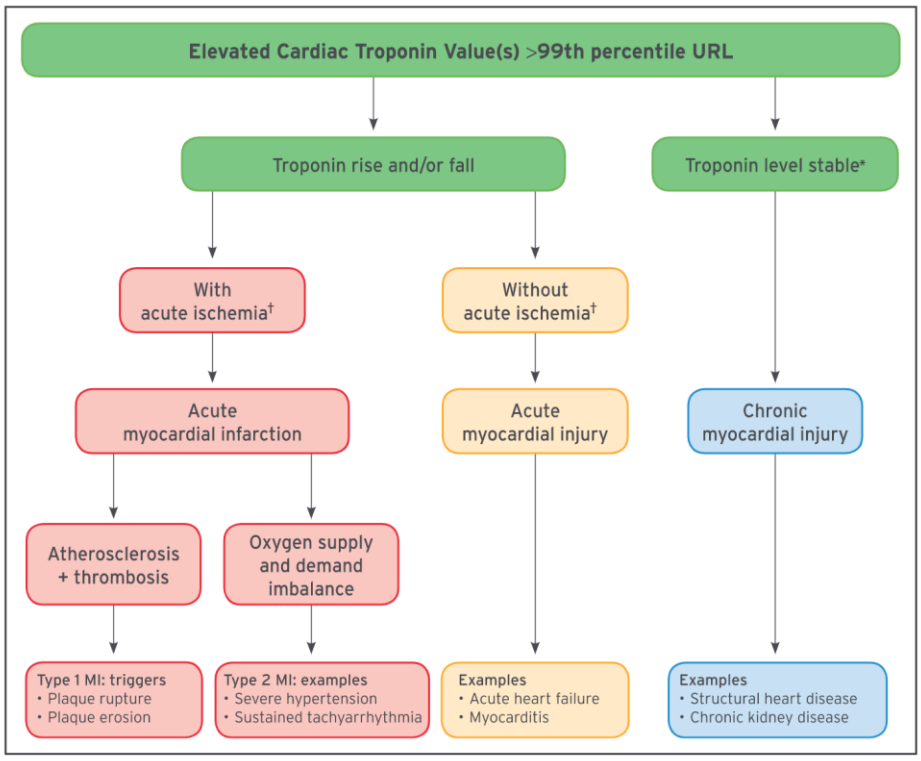

Table 8.3.2: Table from the 4th Universal Definition of Myocardial Infarction summarizing the different definitions of myocardial injury and infarction[99]

2. UNIVERSAL DEFINITIONS OF MYOCARDIAL INJURY AND MYOCARDIAL INFARCTION: SUMMARY

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least 1 value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following:

- Symptoms of myocardial ischemia;
- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for *type 2 MI*. Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure–related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI)–related MI is termed *type 4a MI*.

Coronary artery bypass grafting (CABG)–related MI is termed *type 5 MI*.

Coronary procedure–related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for *type 4a MI* and >10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated preprocedural cTn values, in whom the preprocedural cTn level are stable (≤20% variation) or falling, must meet the criteria for a >5 or >10 fold increase and manifest a change from the baseline value of >20%. In addition with at least 1 of the following:

- New ischemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the prespecified thresholds for PCI and CABG.

Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.

Postmortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any 1 of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of nonischemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology.
- Patho-anatomical findings of a prior MI.

Abbreviations: CABG = indicates coronary artery bypass grafting, cTn = cardiac troponin, ECG = electrocardiogram, MI = myocardial infarction, PCI = percutaneous coronary intervention, URL = upper reference limit.

Myocardial Injury: The increasing sensitivity of cardiac troponin (cTn) assays means that ongoing myocardial injury is frequently detected. Myocardial injury are necessary to make the diagnosis of MI. Adjudicators must distinguish between acute myocardial injury that is not secondary to ischemia but may be due to other conditions (Table 8.3.1).

Criteria for Myocardial injury: Detection of an elevated cTn value above the 99th percentile upper reference limit (URL) is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.[99]

Criteria for Procedure Related Myocardial Injury:

Cardiac procedural myocardial injury is arbitrary defined by increased in cTn values (>99thpercentile URL) in patients with normal baseline values (<99thpercentile URL) or a rise of cTn values >20% of the baseline value when it is the above the 99thpercentile URL but is stable or falling.

Myocardial Infarction Type 1: Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- New ischemic ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy†
- *ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):
    - ST Elevation: New ST elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V2-V3, where the following cut-points apply: ≥2mm in men ≥40 years; ≥2.5 mm in men <40 years; or ≥ 1.5 mm in women regardless of age.
    - ST-depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.5 mm in 2 contiguous leads and/or T inversion ≥ 1 mm in two contiguous leads with prominent R waves or R/S ratio >1.
- **Pathological Q waves:
    - Any Q-wave in leads V2-V3 >0.02 seconds or QS complex in leads V2-V3○Q-wave ≥ 0.03 seconds and ≥1 mm deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any 2 leads of a contiguous lead grouping (I, aVL;V1-V6; II, III, aVF; V7-V9).
    - R-wave ≥ 0.04s in V1–V2 and R/S ≥ 1with a concordant positive T-wave in the absence of a conduction defect
- †Postmortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large, circumscribed area of necrosis with or without intramyocardial hemorrhage meets the type 1 MI criteria regardless of cTn values.
- Consideration will be given to recent proposals to modify myocardial infarction type 1 to include coronary obstruction by spontaneous coronary artery dissection, coronary embolism, or coronary vasospasm or microvascular dysfunction.[98]

Table 8.3.1: Causes of non-ischemic myocardial injury[95,100]

Heart failure
Myocarditis
Cardiomyopathy
Takotsubo syndrome
Coronary revascularization procedure
Cardiac procedure other than revascularization

Catheter ablation
Defibrillator shocks
Cardiac contusion
Sepsis, infectious disease
Chronic kidney disease
Stroke, subarachnoid hemorrhage
Pulmonary embolism, pulmonary hypertension
Infiltrative disease, e.g., amyloidosis, sarcoidosis
Chemotherapeutic agents
Critically ill patients
Strenuous exercise
Other

Myocardial Infarction Type 2: Detection of a rise and/or fall of cTn values with at least 1 value above the 99thpercentile URL, and evidence of imbalance between myocardial oxygen supply and demand unrelated to coronary atherothrombosis, requiring at least 1 of the following:

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemic etiology

Myocardial Infarction Type 3: Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Myocardial infarction Type 4a and 4b (myocardial infarction associated with percutaneous coronary intervention): Criteria for percutaneous coronary intervention (PCI)-related MI ≤48 hours after the index procedure are as follows: Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values >5 times the 99the percentile URL in patients with normal baseline values. In patients with elevated preprocedural cTn in whom the cTn levels are stable (≤20% variation) or falling, the post procedure cTn must rise by >20%. However, the absolute procedural value must still be at least 5 times the 99th percentile URL. In addition, 1 of the following elements is required:

- New ischemic ECG changes
- Development of new pathological Q waves; note that the development of new pathological Q waves meets the criteria for procedure-related MI if the cTn values are elevated and rising but <5 times the 99th percentile URL.

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.
- Type 4a MI is an MI associated with PCI
- Type 4b MI is an MI associated with stent/scaffold thrombosis

Myocardial Infarction Type 4c: A type 4c MI is an MI associated with restenosis associated with prior PCI. Possible Type 4c MI is evaluated using the same criteria as Type 1 MI.

Myocardial Infarction Type 5: Criteria of coronary artery bypass grafting (CABG)-related MI ≤ 48 hours after the index procedure. CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99thpercentile URL in patients with normal baseline cTn values. In patients with elevated preprocedural cTn in whom cTn are stale (≤20% variation) or falling, the post procedure cTn must rise by >20%. However, the absolute postprocedural values must still be >10 times the 99thpercentile URL. In addition, one of the following elements is required:

- Development of new pathological Q waves; note that the development of new pathological Q waves meets the criteria for procedure-related MI if the cTn values are elevated and rising but <10 times the 99thpercentile URL.
- Angiographically documented new graft occlusion or new native coronary artery occlusion; Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

Special or unusual circumstances: Further guidance on distinguishing myocardial injury from myocardial infarction in the context of non-cardiac surgery, heart failure, myocarditis, Takotsubo syndrome, kidney disease, and in critically ill patients, and myocardial infarction nonobstructive coronary arteries is included in the 4th Universal Definition of MI.[99]

Stroke

The definition of stroke used here is drawn from the definitions proposed by Hicks et al. and Sacco et al.8,9Stroke is defined as the acute onset of focal neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

A stroke is the acute onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow with no apparent nonvascular cause (e.g., tumor, trauma, infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. To the extent possible, all strokes will be classified as ischemic, hemorrhagic, or unknown.

For the diagnosis of stroke, the following criteria should be fulfilled:

(1) Rapid onset of a focal neurological deficit not related to any other known non-cerebrovascular process with at least one of the following:

- Change in level of consciousness
- Hemiplegia
- Hemiparesis
- Numbness or sensory loss affecting one side of the body
- Dysphasia/aphasia
- Hemianopia
- Other new neurological sign/symptom(s) consistent with stroke
- If the timing of onset is uncertain, a diagnosis of stroke may be made provided that there are no plausible non-stroke causes for the clinical presentation.

AND

(2) Duration of a focal/global neurological deficit that is:

- EITHER ≥ 24 hours,
- OR < 24 hours if:
    - Resolution of symptoms is due to least one of the following interventions:
        - 1. Pharmacologic: intravenous or intraarterial thrombolysis
        - 2. Non-pharmacologic: (i.e., neuro-interventional procedure such as intracranial angioplasty)
    - OR available MRI clearly documents a new hemorrhage or infarct.
    - OR available head CT clearly documents a new hemorrhage or infarct or excludes a mimic of stroke.
    - OR the neurological deficit results in death.

Ideally, at least one of should be present to confirm the diagnosis of stroke:

- Confirmation by neurology or neurosurgery specialist
- Brain imaging procedure (at least one of the following): CT scan, MRI scan, or cerebral vessel angiography
- Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)

If the acute focal signs represent a worsening of a previous deficit, these signs must persist for more than 24 hours and be accompanied by an appropriate new MRI or CT scan finding.

Strokes are sub-classified as follows:

Ischemic (non-hemorrhagic): An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke but would also be listed as a major bleeding safety event.

Hemorrhagic: An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. Hemorrhage in the brain is documented by neuroimaging or autopsy or lumbar puncture. Note that subdural hematomas are intracranial hemorrhagic events and not strokes.

Undetermined: An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

8.4 Major Bleeding definitions

Adapted from the supplementary appendix of from the original ATTACC/ACTIV-4a/REMAP-Cap trial report and are based on guidelines from ISTH[10,96,101].

Major Bleeding

Major bleeding was defined as acute clinically overt bleeding associated with one or more of the following (as per ISTH guidelines):[96,101]

- Decrease in hemoglobin of 2 g/dL or more;
- Transfusion of 2 units or more of packed red blood cells;
- Bleeding that occurs in at least one of the following critical sites:
    - Intracranial
    - Intraspinal
    - Intraocular (within the corpus of the eye. A conjunctival bleed is not an intraocular bleed)
    - Pericardial
    - Intraarticular
    - Retroperitoneal
    - Intramuscular with compartment syndrome
- Bleeding that leads to death (primary cause of death or contributes directly to death)

8.5 Study Protocols

8.5.1 Inclusion/Exclusion Criteria

Adapted from the supplementary appendix of from the original ATTACC/ACTIV-4a/REMAP-Cap trial report and the ATTACC protocol[10,102].

ATTACC

Inclusions:

1. Patients ≥18 years of age providing (possibly through a substitute decision maker) informed consent who require hospitalization anticipated to last ≥72 hours, for microbiologically confirmed COVID-19, enrolled < 72 hours of hospital admission or of COVID-19 confirmation

Exclusions:

1. Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization
2. Patients for whom the intent is to not use pharmacologic thromboprophylaxis
3. Active bleeding
4. Risk factors for bleeding, including:
    a. intracranial surgery or stroke within 3 months;
    b. history of intracerebral arteriovenous malformation;
    c. cerebral aneurysm or mass lesions of the central nervous system.
    d. intracranial malignancy
    e. history of intracranial bleeding
    f. history of bleeding diatheses (e.g., hemophilia)
    g. history of gastrointestinal bleeding within previous 3 months
    h. thrombolysis within the previous 7days
    i. presence of an epidural or spinal catheter
    j. recent major surgery <14days
    k. uncontrolled hypertension (sBP >200mmHg, dBP >120mmHg)
    l. other physician-perceived contraindications to anticoagulation
5. Platelet count <50 x109/L, INR >2.0, or baseline aPTT>50
6. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur)
7. Acute or subacute bacterial endocarditis
8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity
9. Current use of dual antiplatelet therapy
10. Patients with an independent indication for therapeutic anticoagulation
11. Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention
12. Anticipated transfer to another hospital that is not a study site within 72hours
13. Enrollment in other trials related to anticoagulation or antiplatelet therapy

ACTIV-4a

Inclusion Criteria:

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- ≥ 18 years of age
- Hospitalized for COVID-19*
- Enrolled within 72 hours of hospital admittance or 72 hours of positive COVID test
- Expected to require hospitalization for > 72 hours

*It is strongly recommended to confirm SARSCoV2 with a positive microbiological test prior to randomization. At centers where there in confirming the diagnosis, a sufficiently high clinical suspicion is sufficient to proceed with randomization as long as confirmation is expected within 24 hours.

Exclusion Criteria:

- Platelets < 50x 10_9/L
- Hemoglobin <80 g/L (8 g/dL)
- History of heparin-induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity
- Patient on dual antiplatelet therapy, when one of the agents cannot be stopped safely
- Imminent death
- Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization
- Co-enrollment in other trials is permitted as long as the other trial does not test agents with antithrombotic properties and there is no other scientific contraindication
- Contraindication to anticoagulation, including but not limited to:
    - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
    - known history of an inherited or active acquired bleeding disorder
    - recent ischemic stroke
- Pregnancy

8.5.2 Treatments

ATTACC

Participants randomized to the investigational arm will receive therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from the need for supplemental oxygen, whichever comes first) with preference for low-molecular weight heparin (LMWH), or alternative unfractionated heparin (UFH).

Participants randomized to the control arm will receive usual care venous thromboprophylaxis, which is anticipated to include thromboprophylactic dose anticoagulation according to local practice.

ACTIV-4a

Study Intervention

Any of the following strategies are recommended for therapeutic-dose anticoagulation:

Table 8.5.2.1: Therapeutic-Dose Anticoagulation[a]

CrCl (mL/min)	BMI (kg/m^2)	Enoxaparin	Dalteparin	Tinzaparin	Heparin
≥30	<40	1 mg/kg SC q12h OR 1.5 mg/kg SC q24h	200 units/kg SC q24h OR 100 units/kg SC q12h	175 units/kg SC q24h	IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values[b]
	≥40	1 mg/kg SC q12h	100 units/kg SC q12h		
<30	<40	Heparin IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values*			
	≥40				

Abbreviations: aPTT = activated partial thromboplastin clotting time, BMI = body mass index, CrCl = creatinine clearance, IU = international units, IV = intravenous, SC = subcutaneous

[a]Initial bolus dose determined by sites, encouraging use of dosing algorithm designed for treatment of VTE. UFH anti-Xa titration is preferred over aPTT if available because achieving a therapeutic aPTT may be challenging in patients with a pro-inflammatory state such as COVID-19.

[b]These drugs are considered standard of care as anticoagulants. Different drugs are used in different regions, countries, and hospital formularies. In this pragmatic trial of antithrombotic therapy in COVID-19, sites will use the anticoagulant that they typically use in the hospital setting.

Note: Tinzaparin commonly used in Canada

Note: Fondaparinux not advised in this setting due to its long half life

It is recommended that participants be given therapeutic-dose parenteral anticoagulation daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may continue beyond 14 days at the discretion of the most responsible physician. At the time of treatment discontinuation, standard of care antithrombotic prophylaxis should be administered.

If there is transfer to ICU level care, continue assigned treatment unless there are contraindications.

Discontinuation of study intervention:

Patients randomized based on suspicion of COVID 19 whose tests do not confirm SARS CoV2 infection should not continue to receive study assigned therapeutic-dose anticoagulation.

Anticoagulation should be discontinued if there is clinical bleeding or other complications sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is a severe adverse event (SAE). Assigned treatment may be resumed if deemed appropriate by the treating clinician.

Occurrence of HIT must result in the cessation of UFH or LMWH without recommencement regardless of treatment assignment. The use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE.

Study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible, but not longer than 24 hours – such as to allow surgical or other procedures is not a protocol deviation. Temporary or permanent cessation of study intervention for bleeding is not a protocol deviation.