Thrombosis in COVID 2022: An Updated Narrative Review of Current Literature and Inpatient Management

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ABSTRACT

Early in the pandemic, it was recognized that infection with COVID-19 was associated with an increased incidence in both venous and arterial thrombotic events leading to poor patient outcomes. Given the rapid rise of the pandemic, anticoagulation strategies were initially based upon retrospective and observational data with few high-quality randomized control trials to help direct strategies regarding the use of thromboprophylaxis during hospitalization, empiric therapeutic anticoagulation, and extended-duration thromboprophylaxis after discharge. Over the past year, several randomized control trials have now been published evaluating these strategies. In this article, we hope to review the current literature surrounding the use of intermediate-dose thromboprophylaxis, empiric therapeutic anticoagulation, and the use of extended-duration thromboprophylaxis for patients hospitalized with COVID-19.

KEYWORDS: Coronavirus 2022, COVID-19, COVID-19 coagulopathy, thrombosis, anticoagulation

INTRODUCTION

Early literature regarding Coronavirus 2019 (COVID-19) described derangements in coagulation parameters which were associated with poorer patient outcomes.[1-3] Furthermore, post-mortem examination of patients who died from COVID-19 demonstrated direct viral infection of the endothelial cells leading to diffuse endothelialitis, microvascular dysfunction, and widespread thrombotic microangiopathy, raising suspicion that these derangements were markers of thrombotic complications rather than bleeding risk.[4] Clinically, patients hospitalized with COVID-19 were observed to have an increased incidence of venous thromboembolism (VTE) – pulmonary embolism (PE) and deep vein thrombosis (DVT) – and an increased incidence of arterial thromboembolism (ATE) – strokes (CVAs), myocardial infarctions, systemic arterial embolism, and acute limb ischemia.[5-9]

The recognition that thrombosis was a common complication of patients hospitalized with COVID-19, which resulted in poorer patient outcomes, led to the rapid development of strategies to help mitigate thrombotic complications to improve patient outcomes. Tang et al demonstrated improvement in mortality in patients hospitalized with COVID-19 who received thromboprophylaxis with either low-molecular-weight heparin (LMWH) at 40-60mg daily or subcutaneous unfractionated heparin (UFH) at 10,000-15,000 IU daily.[10] This early finding led to the global adoption of prophylactic anticoagulation in the management of patients hospitalized with COVID-19; however, this practice varied between countries and between institutions as some preferred higher intensity thromboprophylaxis, empiric therapeutic anticoagulation for certain populations, and/or extended-duration thromboprophylaxis after discharge. These practices have continuously evolved throughout the pandemic and were initially based upon retrospective and observational data; however, as the pandemic has continued in 2022, results from multiple randomized control trials (RCTs) have emerged to help shape these various practices. The aim of this review is to the summarize the most current literature surrounding the management and prevention of thrombosis in patients hospitalized with COVID-19.

INTERMEDIATE-DOSE PROPHYLAXIS

During the start of the pandemic, the use of intermediate-dose thromboprophylaxis was based upon retrospective studies and meta-analyses examining its use in settings outside of COVID-19. A meta-analysis by Eck et al examined 70 randomized trials investigating intermediate-dose LMWH versus placebo and showed a small but statistically significant improvement in all-cause mortality; however, this benefit was at the cost of an increased rate of major bleeding.[11] Rannuci et al conducted a prospective observational study of 16 ICU patients with COVID-19 and obtained lab work one week after increasing their thromboprophylaxis from standard-dose to intermediate-dose LMWH. Results showed time-related decreases in fibrinogen levels (p=0.001), D-dimer (p=0.02) and improved viscoelastic testing.[12] Another study investigating coagulation profile retrospectively assessed 468 patients with severe COVID-19 who received intermediate-dose prophylaxis (LMWH 40mg twice daily or UFH 7500 IU three times daily) and showed stable or decreasing D-dimer levels in comparison to those who received standard-dose prophylaxis (p<0.001) and an improved 30-day mortality (p=0.045) without differences in bleeding (p=0.1).[13]

There has been a scarcity of new RCTs specifically evaluating the merits of intermediate-dose prophylaxis within the past year. Previously, the INSPIRATION trial was a randomized study examining intermediate-dose LMWH (defined as 1mg/kg daily) versus standard-dose prophylaxis in 660 patients hospitalized with COVID-19 in the intensive care unit (ICU). Intermediate-dose was not associated with benefit – there was no significant difference in 30-day mortality (43.1% vs 40.9%; p=0.50); development of VTEs (3.3% vs 3.5%; p=0.94); ATEs in the form of CVAs (0.3% vs 0.4%; p=0.97); ventilator-free days (30 vs 30 days; p=0.50); or length of ICU stay (5 vs 6 days; p=0.14). Furthermore, there was an increased rate of major bleeds (2.5% vs 1.4%) but did not meet the noninferiority criteria.[14]

Over the past year, INSPIRATION remains the only RCT directly examining the use of intermediate-dose prophylaxis. However, intermediate-dosed prophylaxis has been indirectly examined in other RCTs. HEP-COVID was a trial that evaluated high-risk patients receiving therapeutic LMWH versus intermediate-dose LMWH (30 mg twice daily, 40mg twice daily, or 0.5 mg/kg twice daily) versus standard-dose of LMWH/UFH. The study's primary efficacy outcome (VTE, ATE, or any cause death) and rate of thromboembolism were reduced in non-ICU patient receiving therapeutic dose anticoagulation without differences in rates of major bleeding. The control group was comprised of 38.7% receiving intermediate-dose LMWH, but there was no data specifically comparing the outcomes of those who received intermediate-dose LMWH versus standard-dose LMWH/UFH.[15]

Both the REMAP-CAP for Critically Ill Patients and the ATTACC for the Non-critically Ill Patients trials were specifically investigating the utility of therapeutic-dose heparin, but also incorporated a portion of patients in their control arms who were received intermediate-dose prophylaxis (defined as LMWH 0.5mg/kg twice a day or 40mg twice a day, subcutaneous dalteparin 5000u once daily, UFH 7500 three times daily or 10000 twice daily, or tinzaparin 4500 unit twice daily). In the REMAP-CAP trial, 51.7% of the control group for critically ill patients versus 26.5% for non-critically ill patients in the ATTACC trial received intermediate-dose prophylaxis as per United Kingdom national practice guidelines and was posited as a reason that therapeutic-dose heparin did not show benefit in the critically ill population in the REMAP-CAP trial.[16,17]

Despite more than two years of the COVID-19 pandemic, there continues to be questions regarding the efficacy of intermediate-dose prophylaxis given the lack of prospective RCTs. The INSPIRATION trial demonstrated no improvement in outcomes in ICU patients with a numerical increase in major bleeding events. Given this continued paucity of data, societal guidelines (**Table 1**) from the American Society of Hematology (ASH) and American College of Chest Physicians (CHEST) continue to recommend against its routine use. Meanwhile, the International Society on Thrombosis and Haemostasis (ISTH) states that intermediate-dose could be considered in "high-risk" patients.[18-20]

THERAPEUTIC ANTICOAGULATION

The use of empiric therapeutic anticoagulation has been another strategy in the management of patients hospitalized with COVID-19. To date, the international multiplatform adaptive-design trial which incorporated the ATTACC, REMAP-CAP, and ACTIV-4a trials have collectively examined the use of therapeutic anticoagulation in the largest cohort of patients. REMAP-CAP for Critically Ill Patients was an open-label, RCT comparing the use of therapeutic anticoagulation (defined as LMWH 1mg/kg twice daily or 1.5mg/kg daily, intravenous [IV] UFH, subcutaneous dalteparin 100U/kg twice daily or 200U/kg once daily, or tinzaparin 175 U/kg once daily) versus "usual-care" pharmacologic thromboprophylaxis (defined as standard-dose thromboprophylaxis or intermediate-dose thromboprophylaxis) in patients with severe COVID-19. Severe COVID-19

Table 1. Summary of Societal Recommendations for Thromboprophylaxis in COVID-19[17-19]

	American Society of Hematology (ASH)	International Society for Thrombosis and Haemostasis (ISTH)	American College of CHEST Physicians (ACCP)
Thromboprophylaxis (includes intermediate-dose and therapeutic anticoagulation)	**1) Critically ill:** standard prophylactic-doses over intermediate-intensity or therapeutic-intensity anticoagulation **2) Non-critically ill**: therapeutic-intensity over prophylactic-intensity anticoagulation	Prophylactic-dose UFH or LMWH in acutely ill and/or critically ill COVID-19 patients after assessing bleeding risk. Intermediate-dose LMWH can be considered in high-risk patients. Obese patients defined by actual bodyweight or BMI should consider a 50% increase in the dose of thromboprophylaxis.	Prophylactic-dose anticoagulation in acutely ill and/or critically ill COVID-19 patients over intermediate or full treatment dosing.
Extended-Duration Thromboprophylaxis	No routine anticoagulation post-discharge	Should be considered in patients that meet high-risk criteria. Recommend use of LMWH or DOAC. Duration can be 14–30 days.	Inpatient prophylaxis over inpatient plus extended-duration prophylaxis after discharge.

Red: updated recommendations; NR: no recommendation; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; "critically- ll" defined as patients suffering from a life-threatening condition who would typically be admitted to an intensive care unit (ICU)

was defined by the requirement of any ICU-level respiratory or cardiovascular support (i.e., high-flow nasal cannula, mechanical ventilation, extracorporeal life support (ECMO), vasopressors, or inotropes). This trial enrolled 1098 patients who were administered therapeutic anticoagulation for 14 days or until recovery (defined as discharge or liberation of supplemental oxygen). Ultimately, there was no difference between the experimental and control group in its primary endpoint of 21-day organ support-free days or survival to hospital discharge (40.1% vs 41.1%, respectively). Of note, the therapeutic arm was also associated with a higher percentage (3.8% vs 2.3%) of major bleeding events leading to the premature closure of the trial. Authors theorized that potential reasons for the lack of positive results included poor adherence to therapeutic anticoagulation in the treatment arm – only 77.6% of patients receiving therapeutic levels of anticoagulation. Furthermore, the authors noted that in the control arm, 51.7% patients receiving intermediate-dose anticoagulation, which may have comparatively limited the benefit of therapeutic anticoagulation.[17] These results differed from an earlier randomized trial, HESACOVID, which was an open-label, phase II RCT examining the empiric use of therapeutic LMWH 1mg/kg twice daily versus standard prophylaxis (defined as subcutaneous UFH 5000 IU three times daily or LMWH 40 mg daily) in 20 mechanically ventilated COVID-19 patients and showed that therapeutic enoxaparin led to successful 28-day liberation from mechanical ventilation (p=0.031).[21]

ATTACC for Non-critically Ill Patients enrolled 2219 patients with moderate COVID-19 (defined as requiring hospitalization without ICU-level respiratory or cardiovascular support) and were further stratified by D-dimer levels: "high" (defined as ≥ 2x upper limit of normal [ULN]) "low" (defined as < 2x ULN), or unknown. Like the REMAP-CAP trial, patients were administered therapeutic anticoagulation for 14 days or until recovery. However, unlike in the critically ill population, therapeutic anticoagulation showed an improvement in 21-day organ support-free days with a posterior probability of 98.6%. There was also greater survival until hospital discharge without organ support in the therapeutic arm. Patients with "high" D-dimer levels had a posterior probability for superiority of therapeutic anticoagulation of 97.3%, followed by 92.9% in the "low" cohort, and 97.3% unknown cohort. This suggested greater treatment benefit of therapeutic anticoagulation in non-ICU, COVID-19 patients with high D-dimer levels at time of enrollment. Of note, the average D-dimer level was 3.2x ULN and 1.1x ULN for the "high" and "low" subgroups, respectively. Unlike in REMAP-CAP, intermediate-dose anticoagulation only comprised 26.5% of the control arm.[16]

Aside from the multiplatform ATTACC, REMAP-CAP, and ACTIV-4 trial, there were several other RCTs that examined the use of therapeutic anticoagulation in predominantly non-ICU, COVID-19 patients. The ACTION trial was an open-label trial evaluating 30 days of therapeutic anticoagulation (defined as rivaroxaban 20 mg daily for stable patients, or initial LMWH 1 mg/kg twice per day or IV UFH for unstable patients, followed by rivaroxaban to day 30) against standard-dose prophylaxis with LMWH/UFH. The trial enrolled 615 hospitalized patients with COVID-19 who had symptoms up to 14 days prior to randomization and an elevated D-dimer level at time of enrollment. Ninety-four percent of patients were considered non-critically ill and did not meet criteria for ICU admission. Furthermore, only 27% of patients had a D-dimer level > 3x ULN. The primary efficacy endpoints were time to death, duration of hospitalization, and duration of supplemental oxygen – none of which were different between the therapeutic and prophylactic arms (34.8% vs 41.3%, respectively; p=0.40). However, in the therapeutic arm, there was a statistically significant increased rate of major or clinically relevant non-major bleeding (8% vs 2%, p=0.001).[22]

The open-label RAPID trial investigated the role of therapeutic (defined as LMWH 1mg/kg twice daily or 1.5mg/kg daily, IV UFH, subcutaneous dalteparin 100U/kg twice daily or 200U/kg once daily, or tinzaparin 175U/kg once daily) versus standard-dose prophylaxis for 28 days or until discharge or death in hospitalized, non-ICU, COVID-19 patients. They were also required to either have both supplemental oxygen requirements and an elevated D-dimer level drawn within the first five days of admission, or just an isolated D-dimer level > 2x ULN. A total of 465 patients were enrolled to evaluate a primary composite outcome of death, invasive and non-invasive mechanical ventilation, or admission to ICU. There was no difference between the therapeutic arm and prophylactic in composite primary outcome (16.2 % vs 21.9 %, respectively; p=0.12). Furthermore, analysis of the secondary outcomes showed neither differences in composite of invasive/non-invasive mechanical ventilation (p=0.53), nor in ICU admission (p=0.34). However, there was a decrease in all-cause death in in the therapeutic group (1.8% vs 7.6%, p=0.006). Oddly, the most common cause of death was acute hypoxemic respiratory failure and authors noted that there were no fatal thromboembolic events. Given these findings, it is unclear if the use of therapeutic anticoagulation contributed to the improvement in all-cause death.[23]

HEP-COVID was a RCT that investigated therapeutic LMWH (1 mg/kg twice daily) versus standard and intermediate-dose prophylaxis (UFH up to 22500 IU subcutaneously divided into twice or thrice daily; LMWH 30 mg or 40 mg subcutaneously once or twice daily, or dalteparin, 2500 IU or 5000 IU once daily) in hospitalized ICU and non-ICU patients. Only 34.9% and 30.6% of the therapeutic and non-therapeutic arms, respectively, were ICU patients. In this trial, 253 patients were included if they required supplemental oxygen and either a D-dimer level > 4x ULN on admission or an ISTH sepsis-induced coagulopathy (SIC) score of at least 4. The majority of patients (249 [98.4%]) were enrolled using

the D-dimer criteria. The primary efficacy outcome of VTE, ATE, or death from any cause was decreased in the therapeutic group (p=0.03). This decrease appeared to be driven by thromboembolism (29.0% vs 10.9%, p<0.001) given there was no difference in death (p=0.28). Authors noted that the treatment effect was largely observed within first 14 days of hospitalization. Furthermore, the benefit was seen in non-ICU patients (p=0.004), but not ICU patients (p=0.71). There was no significant difference in major bleeding between the treatment arms, regardless of setting (p=0.12).[15]

Overall, the above trials provide conflicting results regarding the empiric therapeutic anticoagulation. However, several themes do emerge from these multiple trials: 1) there appears to be benefit (21-day organ free support days [ATTACC] or decreased rates of thromboembolism [HEP-COVID]) in hospitalized patients who do not require ICU level of care (i.e., high-flow nasal cannula, mechanical ventilation, ECMO, vasopressors, or inotropes); 2) the largest benefit occurs within the first 14 days of use of therapeutic anticoagulation; and 3) in the non-ICU setting, patients with elevated D-dimers garner the most benefit (though the exact degree of elevation remains unclear).

These themes and remaining questions are reflected in ASH's updated guidelines as they continue to recommend standard-dose prophylaxis for critically ill COVID-19 patients (i.e., requiring ICU level of care), but have updated their guidelines for acutely ill COVID-19 patients (i.e., requiring hospitalization) to now recommending empiric therapeutic anticoagulation over prophylactic anticoagulation. Societal guidelines provided by CHEST and ISTH have not changed in lieu of these new prospective trials.[18-20]

EXTENDED-DURATION PROPHYLAXIS

Given the increased incidence of thrombosis in COVID-19 patients while hospitalized, there was concern for thrombotic complications post-discharge leading to the use of extended-duration thromboprophylaxis. This strategy had been developed in non-surgical patients prior to the pandemic and led to the creation of the modified IMPROVE score (**Table 2**) which stratified patients into risk groups based upon several clinical factors. Patients deemed "high-risk" derived benefit from thromboprophylaxis after discharge.[24,25]

During the first year of the pandemic, data regarding the use of extended-duration thromboprophylaxis was limited to two retrospective studies which observed that patients hospitalized with COVID-19 were not at increased risk for development of VTE when compared to historical cohorts in non-COVID-19 patients from prior retrospective studies.[26,27]

More recently, the MICHELLE trial examined the use of extended-duration thromboprophylaxis. In this trial, patients hospitalized for at least three days with COVID-19 were enrolled if they had a modified IMPROVE score ≥ 4 ("high-risk") or a score of 2–3 with a D-dimer level > 500.

Table 2. Modified IMPROVE Score[24-25]

Risk Factor	VTE Risk Score
Prior VTE	3
Diagnosed thrombophilia*	2
Current lower limb paralysis or paresis**	2
History of cancer†	2
D-dimer > 2 times upper limit of normal	2
ICU or coronary care unit stay	1
Complete immobilization‡ ≥ 1 day	1
Age ≥ 60 years	1

High Risk Score > 4 corresponding with a nearly three-fold higher VTE risk at discharge and warrants consideration for extended-duration VTE prophylaxis; *Congenital or acquired condition leading to increased risk of thrombosis; **Leg falls to bed by 5 seconds but has some effort against gravity (taken from National Institute of Health Stroke Scale); †Cancer present at any time in past five years; ‡Defined as confined to bed or chair with or without bathroom privileges

Of note, 54% and 50% of the treatment and control arms, respectively, were admitted to the ICU. Furthermore, all patients received only standard-dose thromboprophylaxis during their hospitalization. Patients were then randomized to receive rivaroxaban 10mg daily for 35 days or placebo. At 35 days, the use of rivaroxaban led to a decrease in thrombotic events (p=0.0293), mainly in the form of decreased pulmonary embolism when compared to the control arm. Of note, no major bleeding events occurred in either arm.[28] These results suggest that patients hospitalized with COVID-19 with a modified IMPROVE score ≥ 4 or 2–3 with a D-dimer > 500 derive benefit with the use of extended-duration thromboprophylaxis.

CHEST states that extended-duration thromboprophylaxis should be considered for patients at low risk of bleeding. Meanwhile, ASH advises against its routine use for post-discharged patients but does state that patients can be assessed using the modified IMPROVE score to determine if extended-duration thromboprophylaxis is warranted. ISTH states that extended-duration VTE prophylaxis should be considered for patients who are low risk for bleeding who meet high-risk criteria based upon the modified IMPROVE score.[18-20]

CONCLUSION

Over the past two years, the management and treatment of COVID-19 has continued to evolve and change at a dizzying pace – initially guided by limited retrospective data but now guided by high quality evidence garnered from multiple RCTs. The literature surrounding the practice of intermediate-intensity thromboprophylaxis continues to be mostly limited to retrospective data with one RCT (i.e., INSPIRATION) demonstrating no efficacy in ICU patients.[14] The use of empiric therapeutic anticoagulation has received more clarity from multiple RCTs though with some conflicting results. Despite this, several themes have emerged: 1) there

appears to be benefit in patients hospitalized due to COVID-19 who do not require ICU level of care; 2) the largest benefit appears to occur within the first 14 days; and 3) patients with elevated D-dimer levels garner the most benefit (though the exact degree of elevation remains unclear). As far as the use of extended-duration thromboprophylaxis, the MICHELLE trial demonstrated a decreased incidence of post-hospitalization thrombosis in patients hospitalized with COVID-19 after stratification with the modified IMPROVE (score of ≥ 4 or score of ≥ 2–3 with a D-dimer level > 500).[28]

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Disclosures

Conflicts of Interest: The authors declare no conflicts of interest.

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