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COVID-19 Thrombotic Complications and Therapeutic Strategies

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Abstract

Shortly after the emergence of coronavirus disease 2019 (COVID-19) in late 2019, clinicians rapidly recognized an apparent association between the disease and both arterial and venous thrombotic complications, which was confirmed in epidemiologic studies. Based on these data, hospitals empirically developed and implemented protocols with different strategies for anticoagulation of hospitalized COVID-19 patients. Subsequent randomized controlled trials (RCTs) clarified the role of anticoagulation in patients hospitalized with COVID-19 and recently discharged from the hospital. In this review, we discuss the epidemiology and pathophysiology of thrombosis in patients with COVID-19, observational comparative effectiveness analyses that provided hints of a benefit from anticoagulation, and finally the RCTs that established which patients with COVID-19 benefit from treatment-dose anticoagulation. These RCTs have demonstrated that hospitalized, noncritically ill patients with COVID-19 benefit from treatment-dose anticoagulation, but patients who are hospitalized and critically ill, discharged from the hospital, or not hospitalized do not benefit.

INTRODUCTION

Within months of the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a report from the initial coronavirus disease 2019 (COVID-19) epicenter in Wuhan, China reported that 20 of 81 patients (25%) admitted to the intensive care unit (ICU) with COVID-19 pneumonia between January and March 2020 developed venous thromboembolism (VTE) (1). Multiple subsequent reports from the United States and Europe confirmed the high incidence of clinically relevant VTE in critically ill patients, and extended these findings to patients admitted to the general ward (2–10). These studies also documented high rates of arterial thromboembolism, including myocardial infarction, stroke, acute limb ischemia, mesenteric ischemia, coronary stent thrombosis, and thrombosis of dialysis catheters and extracorporeal membrane oxygenation circuits (10). In all studies, the vast majority of patients who developed thrombotic events were treated with either therapeutic- or prophylactic-dose anticoagulation. Other case series noted acute limb ischemia and large vessel stroke in previously healthy younger adults, sometimes as the initial presentation of COVID-19 (11–13).

In these cohort studies, reported rates of arterial and venous thrombotic events were between 17% and 47% in critically ill patients and between 3% and 11% in noncritically ill inpatients (**Table 1**). Most of these studies had substantial limitations—including a lack of standardized outcome definitions, incomplete data capture, single- or oligo-center design, lack of contemporaneous or historical control groups, and highly variable management of anticoagulation—and reported substantially different frequencies of individual arterial and venous thrombotic events. Later, multicenter prospective studies failed to replicate the very high burden of thrombotic events seen in these early studies. In an analysis from the multicenter STOP-COVID (Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19) cohort, which enrolled 3,239 patients admitted to ICUs at 67 US hospitals between March 4 and April 11, 2020, 6.3% of patients developed a VTE, including 5.4% who developed a deep venous thrombosis and 1.0% who developed a pulmonary embolism; 0.6% of patients had an ischemic stroke (14).

Simultaneously, autopsy studies demonstrated that COVID-19 was associated not only with these clinically evident thromboembolic events but also with thrombotic microangiopathy. A series of seven autopsies from Germany demonstrated that patients who died of COVID-19 had evidence of severe pulmonary vascular endothelial injury with intracellular virus and a ninefold greater prevalence of alveolar capillary microthrombi compared with patients who died of influenza (15). Other autopsy studies noted microthrombi in the coronary and renal circulation, though less commonly than in the pulmonary circulation (16, 17). Several studies have attempted to elucidate the pathophysiologic mechanisms by which COVID-19 increases risk of thrombosis, focusing on the elements of Virchow's trial: stasis, hypercoagulability, and endothelial injury. Like all critical illness, COVID-19 increases the likelihood of thrombosis by immobilization (leading to stasis) and inflammation-associated hypercoagulability (18). However, in addition to this more generalized pathway, COVID-19 also directly infects endothelial cells, causing direct endothelial cell injury in vascular beds (19).

COVID-19's particular propensity to cause thrombotic events was confirmed in epidemiologic studies comparing the rate of thrombotic complications in patients with COVID-19 to historical or contemporary controls. A study from New York compared rates of thrombotic complications in patients hospitalized with COVID-19 in March and April 2020 with rates of similar complications in patients hospitalized in the United States for respiratory infections between 2002 and 2014. The study found that 16.0% of patients with COVID-19 had any thrombosis (versus 5.0% of historical controls), 8.9% had myocardial infarction (versus 2.8%), 3.9% had deep venous thrombosis (versus 0.7%), 3.2% had pulmonary embolism (versus 0.8%), 1.6% had ischemic stroke (versus 0.7%), and 1.0% had systemic embolism (versus 0.1%) (20). Though other studies failed to find

Table 1 Early cohort studies reporting the incidence of thrombotic complications in patients hospitalized with COVID-19

Reference	*n*	City	Dates	Any thrombotic event (%)		Deep venous thrombosis (%)		Pulmonary embolism (%)		Myocardial infarction (%)		Stroke (%)	
				ICU	Ward	ICU	Ward	ICU	Ward	ICU	Ward	ICU	Ward
1	81	Wuhan, China	January 30 to March 22, 2020	NR	NR	25.0	NR	NR	NR	NR	NR	NR	NR
4	388	Milan, Italy	February 13 to April 10, 2020	16.7	6.4	4.2	0.3	4.2	2.5	2.1	1.0	6.3	1.9
8	107	Lille, France	February 27 to March 21, 2020	NR	NR	20.6	NR	NR	NR	NR	NR	NR	NR
9	400	Boston, USA	March 1 to April 5, 2020	18.1	4.7	NR	NR	NR	NR	NR	NR	NR	NR
3	3,334	New York, USA	March 1 to April 17, 2020	29.4	11.5	9.4	2.0	6.2	2.2	13.9	7.3	3.7	0.9
5	75	Amsterdam, Netherlands	March 2 to April 12, 2020	47.0	3.3	32.0	1.6	15.0	1.6	NR	NR	NR	NR
6	150	Strasbourg, France	March 3 to 31, 2020	18.0	NR	2.0	NR	16.7	NR	2.6	NR	1.3	NR
10	92	Paris, France	March 6 to April 22, 2022	40.0	NR	13.0	NR	27.0	NR	1.1	NR	2.2	NR
7	184	Leiden, Netherlands	March 7 to April 5, 2020	31.0	NR	NR	NR	NR	NR	0	NR	3.7	NR
2	1,114	Boston, USA	March 13 to April 3, 2020	35.3	2.6	22.9	0	1.8	2.2	7.7	0.5	0.6	0

Abbreviations: ICU, intensive care unit; NR, not reported.

a difference in rates of VTE between COVID-19 patients and either historical or contemporary controls, a systematic review and meta-analysis showed that patients admitted with COVID-19 had an absolute risk of VTE 6% greater than historical or contemporaneous controls with other serious respiratory illness, and patients admitted to the ICU with COVID-19 had an absolute risk of VTE 16% greater than controls (21). There was considerable heterogeneity in these studies, reflecting the diversity of control groups and the differing treatment protocols at different hospitals.

Notably, the increased risk of thromboembolism does not seem to extend to outpatients. In a single-center retrospective analysis, none of 715 patients diagnosed with COVID-19 who were not hospitalized developed an arterial or venous thrombosis (2). Similarly, in a multicenter prospective Iranian registry of 1,529 patients discharged after hospitalization for COVID-19, only 3 patients [0.2%, 95% confidence interval (CI) 0.1–0.6%] had symptomatic VTE in the 45 days after discharge (22). The Iranian finding is similar to the historical incidence of VTE in patients discharged after other acute medical illnesses. Findings were similar in other studies from different geographic regions (23–25).

ESTABLISHING THE ROLE OF ANTICOAGULATION IN PATIENTS WITH COVID-19

The epidemiologic and pathologic evidence of the importance of thromboembolic disease in driving poor COVID-19 outcomes, even among patients on prophylactic doses of anticoagulation, led to considerable interest in alternative antithrombotic regimens. Many hospitals and health systems developed and implemented protocols for empiric anticoagulation of patients with severe COVID-19 using full or half doses. Some of these centers published their experience with these regimens in observational comparative effectiveness studies (26–28); however, observational comparative effectiveness studies cannot account for all of the factors that affect clinicians' decision making and are necessarily subject to confounding by indication (29, 30). As such, randomized controlled trials (RCTs) of antithrombotic regimens for patients with COVID-19 were conducted in three separate settings: prehospital, in-hospital (both in and out of the ICU), and posthospital (**Table 2**).

Antithrombotic Therapy in Outpatients with COVID-19

ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines)-4b was a randomized double-blind placebo-controlled trial of anticoagulant and antiplatelet therapy for the prevention of the composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause in 558 outpatients with symptomatic but stable COVID-19 (31). The trial, conducted from September 2020 through July 2021, was designed to enroll 7,000 patients at 52 US sites. Patients were randomized 1:1:1:1 to placebo, aspirin 81 mg daily, prophylactic-dose apixaban (2.5 mg twice daily), or therapeutic-dose apixaban (5 mg twice daily). The trial was conducted remotely with limited face-to-face contact with trial participants, who gave informed consent electronically and had trial drugs mailed to them. Median time from diagnosis to randomization was 7 days and from randomization to study treatment initiation was 3 days. Ultimately, the trial was terminated early due to lower than anticipated event rates. At the time the trial was stopped, only 3 of 558 patients had primary endpoint events (0.5%), without differences between groups. These results, combined with observational data showing a very low rate of VTE in COVID-19 patients managed as outpatients, indicate that anticoagulation and antiplatelet therapy may not be beneficial for outpatients with COVID-19. However, as patients in ACTIV-4b had a long delay from diagnosis to receipt of study drug, it is possible that earlier initiation of antithrombotic therapy may be beneficial, especially for the subgroup of patients at high risk of hospitalization;

Table 2 Major randomized clinical trials of antithrombotic regimens in patients hospitalized with COVID-19

Trial (reference)	*n*	Higher-intensity regimen	Lower-intensity regimen	Primary efficacy outcome	Event rate		OR (95% CI) for primary efficacy outcome, high versus low	Primary safety outcome	Event rate		OR (95% CI) for primary safety outcome, high versus low
					High	Low			High	Low	
Critically ill											
INSPIRATION (32)	562	Enoxaparin 1 mg/kg daily (intermediate dose)	Enoxaparin 40 mg daily (prophylactic dose)	Arterial or venous thrombosis, ECMO, or death at 30 days	45.7%	44.1%	1.06 (0.76–1.48)	BARC 3–5 bleeding	2.5%	1.4%	1.83 (0.53–5.93)
Perepu et al. (33)	176	Enoxaparin 1 mg/kg daily (intermediate dose)	Enoxaparin 40 mg daily (prophylactic dose)	30-day all-cause mortality	14.9%	20.9%	0.66 (0.30–1.45)	ISTH major bleeding	2.3%	2.3%	0.99 (0.14–7.14)
REMAP-CAP, ACTIV-4a, ATTACC (35)	1,098	Therapeutic dose anticoagulation, i.e., enoxaparin 1 mg/kg twice daily, continuous intravenous heparin infusion	Prophylactic dose (i.e., enoxaparin 40 mg daily, subcutaneous heparin 5,000 units twice daily)	Organ support–free days	1 (IQR −1 to 16)	4 (IQR −1 to 16)	0.83 (0.67–1.03)	ISTH major bleeding	3.8%	2.3%	1.48 (0.75–3.04)
Hospitalized but not critically ill											
REMAP-CAP, ACTIV-4a, ATTACC (36)	2,219	Therapeutic dose anticoagulation, i.e., enoxaparin 1 mg/kg twice daily, continuous intravenous heparin infusion	Prophylactic dose (i.e., enoxaparin 40 mg daily, subcutaneous heparin 5,000 units twice daily)	Proportion of patients with no days of organ support over 21 days	19.8%	23.6%	0.79 (0.63–0.97)	ISTH major bleeding	1.9%	0.9%	1.80 (0.90–3.74)
ACTION (39)	614	Rivaroxaban 20 mg daily × 30 days	Prophylactic dose (i.e., enoxaparin 40 mg daily, subcutaneous heparin 5,000 units twice daily)	Time to death, duration of hospitalization, or duration of supplemental oxygen, as assessed by win ratio	34.8% wins	41.3% wins	0.86 (0.59–1.22)	ISTH major or clinically relevant non major bleeding	8.4%	2.3%	3.64 (1.61–8.27)

(*Continued*)

Table 2 (*Continued*)

Trial (reference)	*n*	Higher-intensity regimen	Lower-intensity regimen	Primary efficacy outcome	Event rate		OR (95% CI) for primary efficacy outcome, high versus low	Primary safety outcome	Event rate		OR (95% CI) for primary safety outcome, high versus low
					High	Low			High	Low	
RAPID (37)	465	Therapeutic dose heparin (i.e., enoxaparin 1 mg/kg twice daily)	Prophylactic dose heparin (i.e., enoxaparin 40 mg daily)	28-day death, invasive mechanical ventilation, noninvasive mechanical ventilation, or ICU admission	16.2%	21.9%	0.69 (0.43–1.10)	ISTH major bleeding	0.9%	1.7%	0.52 (0.09–2.85)
HEP-COVID (38)	253	Enoxaparin 1 mg/kg twice daily	Prophylactic or intermediate dose heparin per local institutional standard	Arterial or venous thrombosis or all-cause death at 30 days	28.7%	41.9%	0.68 (0.49–0.96)	ISTH major bleeding	4.7%	1.6%	2.88 (0.59–14.02)
BEMICOP (40)	65	Bemiparin 115 units/kg daily	Bemiparin 3,500 units daily	Death, ICU admission, need for mechanical ventilation, development of moderate to severe respiratory distress, or venous or arterial thrombosis at 10 days	21.9%	18.2%	1.26 (0.37–4.26)	ISTH major or clinically relevant nonmajor bleeding	0	0	–
ACTIV-4a (44)	562	Therapeutic dose heparin + $P2Y_{12}$ inhibitor	Therapeutic dose heparin alone	Organ support–free days at 21 days	21 (IQR 20–21)	21 (IQR 21–21)	0.83 (0.55–1.25)	ISTH major bleeding	2.0%	0.7%	3.31 (0.64–17.20)
RECOVERY (45)	14,892	Aspirin 150 mg daily	Usual care	28-day mortality	16.6%	17.2%	0.96 (0.89–1.04)	Intracranial bleeding or bleeding requiring transfusion, surgery, or vasoactive drugs	1.6%	1.0%	1.55 (1.16–2.07)

(*Continued*)

Table 2 (*Continued*)

Trial (reference)	*n*	Higher-intensity regimen	Lower-intensity regimen	Primary efficacy outcome	Event rate		OR (95% CI) for primary efficacy outcome, high versus low	Primary safety outcome	Event rate		OR (95% CI) for primary safety outcome, high versus low
					High	Low			High	Low	
Post-discharge extended thromboprophylaxis											
MICHELLE (46)	320	Rivaroxaban 10 mg daily × 35 days	Placebo	Symptomatic or fatal VTE, asymptomatic VTE on lower-limb venous ultrasound and CT pulmonary angiogram, symptomatic arterial thrombosis, or cardiovascular death at 35 days	3.1%	9.4%	0.33 (0.12–0.90)	ISTH major bleeding	0	0	–

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; ISTH, International Society for Thrombosis and Hemostasis; OR, odds ratio; VTE, venous thromboembolism.

Table 3 Major ongoing trials of antithrombotic regimens in patients with COVID-19

Trial (National Clinical Trials identifier)	Population	Arms
APOLLO (NCT04746339)	1,000 community-dwelling COVID-19 patients at high risk for thrombotic events	Apixaban 2.5 mg twice daily versus placebo for 30 days
PREVENT-HD (NCT0450823)	4,000 community-dwelling COVID-19 patients at high risk for thrombotic events	Rivaroxaban 10 mg daily versus placebo for 35 days
ETHIC (NCT04492254)	1,370 community-dwelling, unvaccinated COVID-19 patients at high risk for severe disease	Prophylactic enoxaparin versus standard of care (no anticoagulation) for 21 days
CARE (NCT04757857)	660 community-dwelling COVID-19 patients at high risk for severe disease	Rivaroxaban 10 mg daily versus standard of care (no anticoagulation) for 14 days
COVID-PACT (NCT04409834)	750 critically ill COVID-19 patients	2 × 2 factorial: 1) full-dose versus prophylactic dose anticoagulation; 2) clopidogrel versus no clopidogrel
IMPACT (NCT04406389)	186 critically ill COVID-19 patients	Therapeutic-dose versus intermediate-dose anticoagulation
FREEDOM COVID (NCT04512079)	3,600 hospitalized, noncritically ill COVID-19 patients	Prophylactic enoxaparin versus therapeutic-dose enoxaparin versus apixaban 5 mg twice daily
HERO-19 (NCT04542408)	172 hospitalized, noncritically ill COVID-19 patients	Therapeutic-dose enoxaparin (while hospitalized) plus edoxaban 60 mg daily (after discharge) versus prophylactic-dose enoxaparin (while hospitalized only)
ACTIV-4c (NCT04650087)	5,320 patients discharged from the hospital after COVID-19 diagnosis	Apixaban 2.5 mg twice daily versus placebo for 30 days posthospitalization

3.3% of patients enrolled in ACTIV-4b were hospitalized between randomization and receipt of study drug. Ongoing trials may identify a subgroup of outpatients with COVID-19 at high risk for cardiovascular events who benefit from prophylactic anticoagulation doses (**Table 3**).

Antithrombotic Therapy in Inpatients with COVID-19

Several trials have evaluated more or less potent antithrombotic regimens—mostly higher- or lower-dose anticoagulation—in patients hospitalized with COVID-19. Broadly, these trials can be divided into those that enrolled critically ill patients and those that enrolled noncritically ill inpatients.

The first randomized clinical trial of different-intensity anticoagulation regimens in critically ill patients with COVID-19 was the INSPIRATION (Intermediate versus Standard-Dose Prophylactic Anticoagulation in Critically-Ill Patients With COVID-19) trial, which enrolled 562 patients with COVID-19 admitted to the ICU at 10 Iranian hospitals from July to November 2020 (32). These patients were randomized 1:1 to either intermediate-dose anticoagulation (enoxaparin 1 mg/kg daily, with dose adjustments for patients with weight >120 kg or creatinine clearance <30 mL/min) or prophylactic-dose anticoagulation (enoxaparin 40 mg daily, with the same dose adjustments) continued for 30 days regardless of hospitalization status. Intermediate-dose anticoagulation had no significant effect on the incidence of the trial's primary outcome: a composite of centrally adjudicated arterial or venous thrombosis, need for extracorporeal membrane oxygenation, or death within 30 days [odds ratio (OR) 1.06, 95% CI 0.76–1.48]. By

contrast, intermediate-dose anticoagulation significantly increased the risk of Bleeding Academic Research Consortium type 3–5 (major) and type 2 (clinically relevant nonmajor) bleeding.

Perepu et al. (33) tested a similar regimen in a randomized clinical trial enrolling 176 patients with COVID-19 at three US centers from April 2020 through January 2021. To be included, patients had to be hospitalized in the ICU or have an Overt Disseminated Intravascular Coagulation score ≥ 3; 62% of patients were enrolled on the basis of being hospitalized in the ICU (34). Eligible patients were randomized 1:1 to intermediate-dose anticoagulation (enoxaparin 1 mg/kg daily, dose adjusted for obesity) or standard prophylactic-dose anticoagulation (enoxaparin 40 mg daily, dose adjusted for obesity). At 30 days, 13 of 87 patients in the intermediate-dose anticoagulation arm had died (14.9%), compared with 18 of 86 patients in the standard prophylactic-dose arm (20.9%) (OR 0.66, 95% CI 0.30–1.45). There was no difference in major or minor bleeding between the groups.

After these trials reported no difference in efficacy but a higher risk of bleeding with intermediate-dose anticoagulation than with standard prophylactic-dose anticoagulation in critically ill COVID-19 patients, a composite report from the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), ACTIV-4a, and ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) trials compared therapeutic- with prophylactic-dose anticoagulation in patients with COVID-19 requiring ICU-level respiratory or cardiovascular organ support (oxygen by high-flow nasal cannula, noninvasive or invasive mechanical ventilation, extracorporeal life support, vasopressors, or inotropes) (35). Exclusion criteria were imminent risk for death without commitment to full organ support, high risk for bleeding, dual antiplatelet therapy, a separate indication for therapeutic-dose anticoagulation (such as atrial fibrillation or known VTE), or history of heparin sensitivity. REMAP-CAP, ACTIV-4a, and ATTACC were international adaptive platform trials designed to test multiple strategies for treating COVID-19; early in the pandemic, investigators for the three trials harmonized their protocols and statistical analysis plans to study the effect of anticoagulation in patients hospitalized with COVID-19 in one multiplatform clinical trial. Patients were randomized to either parenteral therapeutic-dose anticoagulation or usual-care thromboprophylaxis. Therapeutic-dose anticoagulation was administered according to local site protocols (enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily, dalteparin 100 units/kg twice daily or 200 units/kg daily, tinzaparin 175 anti-Xa units/kg daily, or heparin by continuous infusion) for up to 14 days or until recovery (hospital discharge or discontinuation of supplemental oxygen). Usual-care thromboprophylaxis was defined as either standard low-dose anticoagulation or intermediate-dose thromboprophylaxis according to local clinical practice. The trial began enrollment in April 2020 and was ultimately stopped for futility in December 2020 after the enrollment of 1,207 patients (of whom 1,098 had primary outcome data available) at 393 sites in 10 countries.

The trial's primary outcome, organ support–free days (with patients who died in the hospital assigned a value of -1) through 21 days, did not differ between the therapeutic-dose anticoagulation and usual-care groups (OR 0.83, 95% CI 0.67–1.03), with a point estimate favoring lower-dose anticoagulation. There was similarly no difference in survival to hospital discharge (62.7% versus 64.5%; OR 0.84, 95% CI 0.64–1.11), the composite of major thrombotic events or death (40.1% versus 41.1%; OR 1.04, 95% CI 0.79–1.35), and International Society on Thrombosis and Hemostasis (ISTH) major bleeding (3.8% versus 2.3%; OR 1.48, 95% CI 0.75–3.04). Therapeutic-dose anticoagulation did nominally reduce the incidence of major thrombotic events (6.4% versus 10.4%) and any thrombotic events (7.2% versus 11.1%).

Together, these three trials indicate that therapeutic-dose anticoagulation does not benefit, and potentially harms, critically ill COVID-19 patients. Though these patients have a high rate of thrombotic events, and higher-dose anticoagulation appears to be effective in preventing these

events, their disease process may have progressed too far for them to benefit from higher-intensity thromboprophylaxis. However, as new coronavirus variants emerge and care pathways for critically ill patients with COVID-19 mature, the risk and benefit of anticoagulation for critically ill COVID-19 patients may change.

By contrast, there does appear to be a benefit from therapeutic anticoagulation in hospitalized patients who are not critically ill. The REMAP-CAP, ACTIV-4a, and ATTACC investigators also enrolled a cohort of patients without critical illness, using the same multiplatform design as the trial in critically ill patients (36). This RCT randomly assigned 2,219 patients hospitalized with COVID-19 without critical illness at the time of enrollment to therapeutic-dose anticoagulation (as defined above) or usual-care thromboprophylaxis. Patients were excluded if they had an indication for therapeutic anticoagulation, were being treated with dual antiplatelet therapy, or had a high risk of bleeding. As in the RCT enrolling critically ill patients, the primary outcome was organ support–free days through day 21 after randomization. In the therapeutic anticoagulation group, 19.8% of patients received organ support over 21-day follow-up compared with 23.6% of patients in the usual-care thromboprophylaxis group (OR 0.79, 95% CI 0.63–0.97); the Bayesian posterior probability that therapeutic-dose anticoagulation increased organ support–free days compared with usual-care thromboprophylaxis was 98.6%. Treatment effect did not vary by age, level of respiratory support at enrollment, dose of thromboprophylactic drug, or baseline D-dimer. Therapeutic anticoagulation reduced the composite of major thrombotic event or death (8.0% versus 9.9%; OR 0.72, 95% CI 0.53–0.98), and nominally reduced the risk of major thrombotic event (1.1% versus 2.1%). It did not have a significant effect on progression to intubation or death (10.9% versus 12.1%; OR 0.82, 95% CI 0.63–1.07), in-hospital death (7.3% versus 8.2%; OR 0.83, 95% CI 0.60–1.15), or ISTH major bleeding (1.9% versus 0.9%; OR 1.80, 95% CI 0.90–3.74).

Several smaller trials have tested a similar strategy of therapeutic anticoagulation versus prophylactic anticoagulation with mixed findings (37–40).

The RAPID (Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic) trial was conducted from May 2020 through April 2021 at 28 hospitals in six countries. RAPID enrolled 465 adults with COVID-19 and increased D-dimer levels admitted to hospital wards, and randomized these patients to therapeutic- or prophylactic-dose heparin (37). Nearly all patients were treated with low-molecular-weight heparin (98% of the therapeutic-dose arm and 94% of the prophylactic-dose arm). The trial's primary outcome, a composite of death, invasive mechanical ventilation, noninvasive mechanical ventilation, or admission to an ICU through 28 days, occurred in 16.2% of patients assigned to therapeutic heparin and 21.9% assigned to prophylactic heparin (OR 0.69, 95% CI 0.43–1.10). All-cause death, a key secondary outcome (though one the trial was not powered for), was lower in patients randomized to therapeutic heparin versus prophylactic heparin (1.8% versus 7.6%; OR 0.22, 95% CI 0.07–0.65). ISTH major bleeding occurred infrequently in both groups.

The HEP-COVID trial, conducted from May 2020 through May 2021 at 12 US hospitals, similarly tested therapeutic- versus prophylactic-dose heparin (38). HEP-COVID randomized 253 patients hospitalized with COVID-19 at high risk for thrombosis. Randomization was stratified by ICU or non-ICU status, with 67.2% of patients not admitted to the ICU. The trial's primary outcome, a composite of venous or arterial thromboembolism or all-cause death at 30 days, occurred in 28.7% of patients in the therapeutic-dose heparin arm versus 41.9% of the prophylactic-dose heparin arm (OR 0.68, 95% CI 0.49–0.96). In an analysis stratified by ICU versus non-ICU status, therapeutic-dose heparin reduced the primary outcome in non-ICU patients (36.1% versus 16.7%; OR 0.46, 95% CI 0.27–0.81) but not ICU patients (55.3% versus 51.1%; OR 0.92, 95% CI 0.62–1.39), consistent with the REMAP-CAP, ACTIV-4a, and ATTACC composite RCT. There was a higher incidence of ISTH major bleeding with therapeutic-dose heparin.

In contrast to these trials, the ACTION (Anticoagulation Coronavirus) trial, conducted at 31 sites in Brazil from June 2020 through February 2021, did not show a benefit of therapeutic anticoagulation. ACTION randomized 614 patients with COVID-19 regardless of clinical stability (though 94% were not critically ill) to therapeutic anticoagulation with rivaroxaban 20 mg once daily to be continued for 30 days versus standard prophylactic anticoagulation (84% received enoxaparin 40 mg daily, 13% continued after hospital discharge) (39). The trial's primary outcome, a hierarchical analysis of time to death, duration of hospitalization, or duration of supplemental oxygen, as assessed by the win ratio method, was not different between the therapeutic and prophylactic anticoagulation groups. Therapeutic anticoagulation did nominally reduce the incidence of the composite of VTE, myocardial infarction, stroke, or major adverse limb event (7.4% versus 9.9%; OR 0.75, 95% CI 0.45–1.26); however, ISTH major or clinically relevant nonmajor bleeding occurred more frequently in the therapeutic anticoagulation arm.

Similarly, the BEMICOP (Therapeutic versus Prophylactic Bemiparin in Hospitalized Patients with Nonsevere COVID-19 Pneumonia) trial failed to find a difference in outcomes for patients treated with therapeutic-dose bemiparin (115 units/kg daily) versus standard prophylaxis (3,500 units daily) (40). BEMICOP, conducted at five Spanish hospitals from October 2020 through May 2021, randomized 65 patients with COVID-19 and elevated D-dimer but without critical illness. There was no difference in the trial's primary outcome—the composite of death, ICU admission, need for mechanical ventilation, development of moderate to severe respiratory distress, or venous or arterial thrombosis within 10 days—by trial arm (21.9% versus 18.2%; OR 1.26, 95% CI 0.37–4.26). The trial was stopped early for futility.

The REMAP-CAP/ACTIV-4a/ATTACC, RAPID, and HEP-COVID trials all showed a benefit of therapeutic-dose anticoagulation, while ACTION and BEMICOP did not. The most likely explanation for the difference is the use of different medications. Though ACTION was conducted solely in Brazil and BEMICOP was conducted solely in Spain, both REMAP-CAP/ACTIV-4a/ATTACC and RAPID also enrolled patients in Brazil and Europe, and there was no heterogeneity of outcomes in these trials by region of enrollment (36, 37). In the trials demonstrating the benefit of anticoagulation, therapeutic anticoagulation was achieved either with unfractionated heparin or a low-molecular-weight heparin with a low anti-Xa/anti-IIa ratio; by contrast, ACTION used the selective factor Xa inhibitor rivaroxaban and BEMICOP used bemiparin, a low-molecular-weight heparin with an anti-Xa/IIa ratio of 8:1 (as compared with ~3.5:1 for enoxaparin). In addition to its anticoagulant effects, heparin (including low-molecular-weight heparin) has important anti-inflammatory effects, which are known to differ between heparin preparations (41–43). These anti-inflammatory effects, which may not be present to the same extent with rivaroxaban or bemiparin, may explain part of the benefit of heparin in noncritically ill patients with COVID-19. Several ongoing trials may shed further light on the question of whether therapeutic anticoagulation with non–vitamin K antagonist oral anticoagulants offers benefit in patients hospitalized with COVID-19.

In addition to these trials of different-potency anticoagulation regimens in COVID-19, there have been two trials of antiplatelet agents in patients hospitalized with COVID-19. Between February 2021 and June 2021, the ACTIV-4a investigators randomized 562 noncritically ill patients at 60 hospitals in four countries to therapeutic-dose heparin plus a $P2Y_{12}$ inhibitor (ticagrelor in 63%, clopidogrel in 37%) for 14 days or therapeutic-dose heparin alone (44). The composite primary outcome, organ support–free days up to day 21 after randomization, did not differ between the two arms; the median number of organ support–free days was 21 in both (OR 0.83, 95% CI 0.55–1.25). ISTH major bleeding occurred more frequently in the $P2Y_{12}$ inhibitor arm. The RECOVERY trial enrolled 14,892 patients hospitalized with COVID-19, including those critically and noncritically ill, at 171 hospitals in the United Kingdom and Asia between

November 2020 and April 2021 (45). Patients were randomized to aspirin 150 mg daily or usual care. The trial's primary outcome, 28-day mortality, was 16.6% in the aspirin arm and 17.2% in the usual-care arm [relative risk (RR) 0.96; 95% CI 0.89–1.04]; aspirin had no effect on receipt of invasive mechanical ventilation or the composite of mechanical ventilation or death. Effects were similar regardless of the level of oxygen support at baseline. Aspirin did reduce the risk of a composite of thrombotic events including VTE, stroke, myocardial infarction, or systemic arterial embolism (4.6% versus 5.3%; RR 0.88, 95% CI 0.76–1.01) and increase the risk of major bleeding.

Antithrombotic Therapy in Patients Discharged After Hospitalization for COVID-19

The MICHELLE (Rivaroxaban versus No Anticoagulation for Postdischarge Thromboprophylaxis After Hospitalisation for COVID-19) trial, conducted at 14 centers in Brazil from October 2020 through June 2021, tested a strategy of extended thromboprophylaxis in 320 patients discharged from the hospital after a COVID-19 diagnosis, of whom 52% were hospitalized in the ICU (46). To be included, patients had to have an International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥4 or a score of 2–3 with D-dimer >500 ng/mL (47). Patients were randomized, at the time of hospital discharge, to rivaroxaban 10 mg daily for 35 days after hospital discharge or placebo. The primary outcome was a composite of symptomatic or fatal VTE, asymptomatic VTE on screening bilateral lower-extremity venous ultrasound and computed tomography pulmonary angiography performed at day 35, symptomatic arterial thromboembolism, or cardiovascular death. Extended thromboprophylaxis with rivaroxaban reduced the incidence of the primary outcome by 67%, from 9.4% in the placebo group to 3.1% in the rivaroxaban arm (RR 0.33, 95% CI 0.12–0.90). Rivaroxaban also decreased the incidence of symptomatic events or cardiovascular death (RR 0.11, 95% CI 0.01–0.87). The primary bleeding outcome, ISTH major bleeding, did not occur in any patients.

RECOMMENDATIONS FOR ANTICOAGULATION IN PATIENTS WITH COVID-19

Various national and international organizations have released guidelines for the management of COVID-19; however, most do not comment on strategies for anticoagulation. In line with the trials discussed above, the US National Institutes of Health (NIH) recommends therapeutic-dose heparin, preferentially low-molecular-weight heparin, for hospitalized patients with COVID-19 who have a D-dimer above the upper limit of normal, require low-flow oxygen, and do not have increased bleeding risk (48). Increased bleeding risk is defined, based on clinical trial inclusion and exclusion criteria, as platelet count <50,000, hemoglobin <8 mg/dL, need for dual antiplatelet therapy, known bleeding within the past 30 days resulting in hospitalization or emergency department visit, or known bleeding diathesis. The NIH specifically recommends against the use of oral anticoagulants in hospitalized, noncritically ill patients with COVID-19. For critically ill patients, including those treated with high-flow oxygen, the NIH recommends prophylactic-dose heparin or low-molecular-weight heparin, and against intermediate- or full-dose anticoagulation. For patients who are started on treatment-dose anticoagulation and later transferred to the ICU, NIH guidelines recommend de-escalating to prophylactic-dose anticoagulation. NIH guidelines do recommend against routinely continuing VTE prophylaxis upon discharge, except in the context of a clinical trial, and note that there is insufficient evidence to recommend for or against extended thromboprophylaxis in patients at high risk for VTE and low risk for bleeding. An American Thoracic Society/European Respiratory Society task force document "makes no suggestion for or against continuing prophylactic dose anticoagulant therapy" after discharge (49). NIH guidelines recommend against the use of anticoagulants and antiplatelet therapy for stable outpatients with

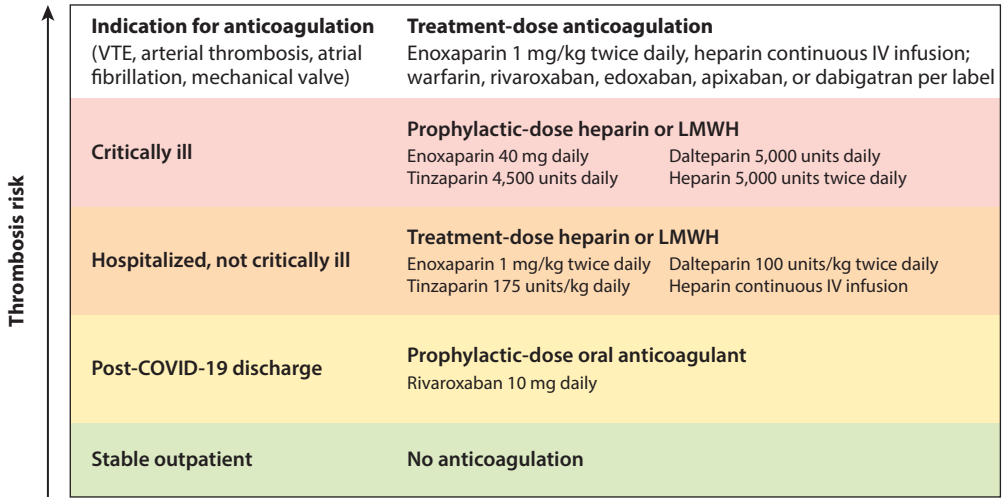

Figure 1

Evidence-based recommendations for anticoagulation in patients with COVID-19. Based on evidence from randomized controlled trials, patients with COVID-19 who are critically ill should be treated with standard prophylactic-dose heparin or LMWH, and hospitalized but noncritically ill patients should be treated with treatment-dose heparin or LMWH but not non–vitamin K antagonist oral anticoagulants. Following discharge, certain high-risk patients may be treated with low-dose rivaroxaban for 35 days to prevent the development of arterial or VTE events. Patients who are not hospitalized at all should not be treated with anticoagulation, as the benefits do not outweigh the risks. Patients with COVID-19 plus another indication for anticoagulation (such as atrial fibrillation or VTE) should receive guideline-directed and evidence-based therapy for this indication regardless of the severity of their COVID-19 illness. Abbreviations: IV, intravenous; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

COVID-19, except in the context of a clinical trial. Among patients with COVID-19 receiving antithrombotic therapy for underlying medical conditions, the NIH recommends continuation of treatment in the absence of the development of significant bleeding or other contraindications.

Taking into account the existing guidelines and the multiple RCTs, as well as the high risk of thrombotic complications in hospitalized patients with COVID-19, we recommend the following treatment strategies, depending on severity of illness (**Figure 1**):

- For stable outpatients with COVID-19, do not use prophylactic or therapeutic anticoagulation except in the context of an RCT (based on ACTIV-4b).
- Hospitalized patients with COVID-19 who (*a*) are not critically ill, (*b*) do not have an indication for anticoagulation, (*c*) are not being treated with dual antiplatelet therapy, and (*d*) are not at high risk of bleeding should receive therapeutic-dose enoxaparin (based on REMAP-CAP, ATTACC, ACTIV-4a, RAPID, and HEP-COVID). Do not use oral anticoagulants except in the context of an RCT (based on BEMICOP and ACTION). Antiplatelet agents are unlikely to improve outcomes and may increase risk of bleeding (based on RECOVERY and ACTIV-4a).
- Hospitalized patients with COVID-19 who are critically ill, including those on high-flow oxygen by nasal cannula, should not receive therapeutic- or intermediate-dose anticoagulation [based on REMAP-CAP, ATTACC, ACTIV-4a, INSPIRATION, and Perepu et al. (33)]. Based on RCTs and consensus guidelines for the management of critically ill patients without COVID-19 (50–52), we recommend treatment with prophylactic-dose anticoagulation in these patients.
- For patients discharged from the hospital at high risk for VTE (IMPROVE VTE score $\geq$4 or 2–3 with D-dimer $>$500 ng/mL), it is reasonable to use rivaroxaban 10 mg daily for 35 days

for extended thromboprophylaxis. This recommendation is based on the MICHELLE trial, as well as five additional trials in patients discharged after a medical illness other than COVID-19 (53).

- For patients with an indication for anticoagulation (including diagnosed VTE, atrial fibrillation, or mechanical prosthetic valve) who have COVID-19 in any setting, use treatment-dose anticoagulation as otherwise indicated.

These recommendations are based on evidence from the multiple completed RCTs of anticoagulation regimens in patients with COVID-19. As ongoing trials are completed, evidence from these trials will need to be incorporated into evidence-based guidelines. Furthermore, as population immunity waxes and wanes in response to infection and vaccination, and as new SARS-CoV-2 variants emerge with higher or lower intrinsic risk of thrombosis, carefully conducted epidemiologic studies will be critical to redefine thrombosis risk and determine the necessity of new RCTs assessing the risks and benefits of different antithrombotic regimens for patients hospitalized with COVID-19.

Regardless, COVID-19's ability to target all three pillars of Virchow's triad—stasis from immobility, hypercoagulability from inflammation, and direct endothelial injury by virus—gives it a unique predisposition among viruses to cause both venous and arterial thrombosis. As such, antithrombotic medications will remain a cornerstone of treatment for seriously ill patients with COVID-19 for the foreseeable future.

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