THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

A Literature Review of Pathophysiology, Clinical Manifestations, Medications and Optimal Dosage, Outpatient, and Post-hospitalization Use of Anticoagulation in COVID-19 Patients

ABSTRACT

Since severe acute respiratory syndrome coronavirus 2 led to a world pandemic, extensive research has been conducted to identify its characteristics and form an appropriate management plan. One recognized complication of COVID-19 is coagulation defects that can lead to thromboembolic events.

We have reviewed the literature to summarize and present the latest research about the pathophysiology, clinical manifestations, anticoagulation use and appropriate dose in COVID-19 patients, as well as the effect of anticoagulation in outpatient and post-hospital settings. The pathophysiology of coagulation abnormalities in COVID-19 is not fully understood yet, but multiple mechanisms appear to be involved, such as a direct viral attack, hyperinflammation, increased immune response, blood stasis, and endothelial injury. Clinical manifestations are mainly venous thromboembolism (deep vein thrombosis and pulmonary embolism), arterial thromboembolism, ischemic stroke, central venous sinus thrombosis, and central retinal vein occlusion. Anticoagulation is widely used in hospitalized patients with COVID-19, unless it is contraindicated. Heparinoid is the main anticoagulant used. However, the appropriate dosage is still debated as research is trying to find a balance between benefits and risks. In outpatients, it appears that anticoagulation has no benefit in contrast to post-hospitalization use, where benefit could be observed in severely affected patients.

We concluded that thromboprophylaxis should be used in treating hospitalized COVID-19 patients, but the dosage is still a matter of debate. More research needs to be done on outpatient and post-hospitalized patients to derive accurate conclusions.

Keywords: Anticoagulation, coagulopathy, COVID-19, heparins, prophylactic anticoagulants

REVIEW

Dimitrios Velissaris[1]
Christos Michailides[1]
Iosif Karalis[1]
Themistoklis Paraskevas[1]
Ioanna Koniari[2]
Charalampos Pierrakos[3]
Vasilios Karamouzos[4]

[1]*Department of Internal Medicine, University Hospital of Patras, Patras, Greece*
[2]*Department of Cardiology, Liverpool Heart and Chest Hospital, Liverpool, UK*
[3]*Department of Intensive Care, Brugmann University Hospital, Université Libre de Bruxelles, Brussels, Belgium*
[4]*Intensive Care Unit, University Hospital of Patras, Patras, Greece*

Corresponding author:
Christos Michailides
✉ christos.mich1@gmail.com

Received: January 23, 2023
Accepted: March 16, 2023
Available Online Date: April 5, 2023

Cite this article as: Velissaris D, Michailides C, Karalis I, et al. A literature review of pathophysiology, clinical manifestations, medications and optimal dosage, outpatient, and post-hospitalization use of anticoagulation in COVID-19 patients. *Anatol J Cardiol.* 2023;27(5):232-239.

DOI:10.14744/AnatolJCardiol.2023.3023

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection triggered a pandemic in 2019; its consequences are obvious until now. Many medications have been tested to improve the outcome of the disease, but only a few have been proven effective. Older patients with comorbidities are the primary candidates for poor outcome. Specific pathways, related to medical conditions that commonly appear to those patients, whose dysfunction leads to poor outcomes, such as coagulation, have been targeted. COVID-19 coagulopathy is a widely talked-about situation that altered the main cure strategies for COVID-19 patients. Herein, we summarize the main pathophysiology, clinical manifestations, medications, dosages, outpatient, and post-hospitalization strategies regarding this condition. Mechanisms that lead to this abnormality are multifarious and include direct viral damage on the endothelium, hyperinflammation that leads to hypercoagulability, blood stasis, and endothelial dysfunction,[1,2] along with patients' condition and the fact that they spend most of their hospital stay bedridden. Clinical manifestations encompass venous thromboembolism (VTE), mostly deep vein thrombosis (DVT) and pulmonary embolism (PE), arterial thrombosis and peripheral limb ischemia, and ischemic stroke and central venous sinus thrombosis.[2,3] It is

established that anticoagulation treatment reduces in-hospital mortality and thrombotic incidents.[4] Medications used are heparins (unfractionated (UFH), low-molecular-weight heparin (LMWH), fondaparinux),[5] apixaban,[6] rivaroxaban,[7] and antiplatelet drugs.[8] Standard prophylactic dose, intermediate, and kg-based therapeutic doses have been examined, composing a broken glass between risks and benefits of each.[9] Outpatient and post-hospitalization anticoagulation treatment strategies are still investigated, but it seems that outpatient anticoagulation has no benefit in contrary to post-hospitalization use of oral anticoagulants.[10,11]

PATHOPHYSIOLOGY

One of the main complications of COVID-19 is coagulation defects, which are characterized by micro-thrombotic patterns mainly in the lung.[12-14] Nevertheless, the mechanism of this defect is not fully understood.[15] Coagulation abnormalities appear to be caused by the direct viral attack, hyperinflammation, and high immune response to the virus infection, stasis, and endothelial dysfunction.[1,2] Direct viral attack on the endothelial cells causes cell injury that activates primary and secondary pathways of hemostasis, and at the same time, it suppresses anticoagulation activity.[16] The endothelial cell endothelitis and diffuse endothelial inflammation create endothelial disruption that triggers the proinflammatory and procoagulant pathways.[17-19] Research on COVID-19 coagulopathy defines that SARS-CoV-2 may promote pulmonary coagulopathy by directly affecting bronchial epithelial cells and activating tissue factor signaling.[20] In response to the virus infection, the respiratory epithelium triggers inflammatory and immune reactions with alveolar infiltration of the leucocytes and the release of chemokines and cytokines.[12,20] This initiates an inflammatory response, locally in the lungs and then systemically.[21] The most severely affected patients can develop a so-called cytokine storm characterized by high proinflammatory cytokines and chemokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α).[1,16,22,23] This significant inflammatory state and cytokine production, evident by high C-reactive protein (CRP) and ferritin, activate the endothelium that, in turn, activates the coagulation pathway causing hypercoagulability.[1,17,21,24,25] A-defensins, complement products, and CRP, activated by the activated neutrophils and secreted IL-6, have prothrombotic action as well, contributing to a prothrombotic state.[16,20,22,26] At the same time, hyperinflammation inhibits the regulatory mechanisms of coagulation by increased degradation of antithrombin through enzymes that are abundant in neutrophils.[16] Moreover, intermittent hypoxia due to pneumonia can induce the release of tissue factors by the endothelial cells and activate the extrinsic coagulation cascade.[23] Another essential factor that contributes to hypercoagulability is the hyperviscosity that has been observed in COVID-19 patients. Fibrinogen and clotting factors are significant contributors to hyperviscosity. It has been observed that higher levels of these 2 in a patient affected by SARS-CoV-2 cause hyperviscosity and, to an extent, hypercoagulability.[17]

It is well known that COVID-19 is attached to angiotensin-converting enzyme 2 (ACE II) receptors on endothelial cells. This leads to excess levels of angiotensin II. Angiotensin II binds to the angiotensin receptor I and enhances the coagulation cascade by increasing cytokine levels and inducing plasminogen activator inhibitor-1 on endothelial cells.[21] In addition, dysfunction of the Renin–Angiotensin–Aldosterone System induces inflammatory responses that enhance inflammation.[16] Angiotensin-converting enzyme II receptors are also located beyond the lung, such as in the brain's endothelium and vascular smooth muscle cells, which could potentially explain thrombotic phenomena in other organ systems.[2] In addition, some studies showcased that cardiac fibroblast may play a role in micro-thrombi formation in the heart.[27]

All the above, in combination with prolonged immobilization during critical illness, mechanical ventilation, central venous catheterization, and surgery, as well as predisposing risk factors for endothelial damage such as hypertension and diabetes mellitus, may cause an accumulation of VTE risk that may lead to endothelial vascular damage, endothelitis, and induce thrombosis[15,16,17,28] (Figure 1).

HIGHLIGHTS

- COVID-19-induced thrombosis is related to microthrombosis, hyperinflammation, and endothelial dysfunction.
- COVID-19 patients are at increased risk of arterial thromboembolism, deep vein thrombosis, pulmonary embolism, central venous thrombosis, and stroke.
- Unfractionated heparin, low-molecular-weight heparin, direct oral anticoagulants, and nonoral direct anticoagulants but not antiplatelet drugs improve outcomes of hospitalized COVID-19 patients due to preventing thrombosis.
- The optimal dosage is not yet determined, but standard prophylactic anticoagulation is recommended for all hospitalized COVID-19 patients.
- Intermediate and therapeutic dosages are debatable and treatment should be individualized according to risks and benefits for each patient.

CLINICAL MANIFESTATIONS

Severe acute respiratory syndrome coronavirus 2 infection pathophysiology leads to increased prevalence of VTE, peripheral arterial thromboembolism (ATE), ischemic stroke, and central venous sinus thrombosis.[2,3] Among intensive care unit (ICU) patients, prevalence seems to be even higher.[19] Venous thromboembolism mostly refers to PE and DVT. Birocchi et al compared COVID-19 and non-COVID-19 patients screened for DVT and PE with ultrasound (US). COVID-19 patients had 15.43% prevalence of DVT and 4.85% prevalence of PE, while non-COVID-19 patients were significantly less consulted (4.21% and 0.22%, respectively).[13] Differences in diagnostic methods for VTE among the studies result in wide heterogeneity in referred prevalence. When diagnosis did not include US screening for VTE, overall pooled prevalence was 21% for VTE, 15% for PE, and 27% for DVT.[29] In patients screened with US, prevalence was 32% for PE and

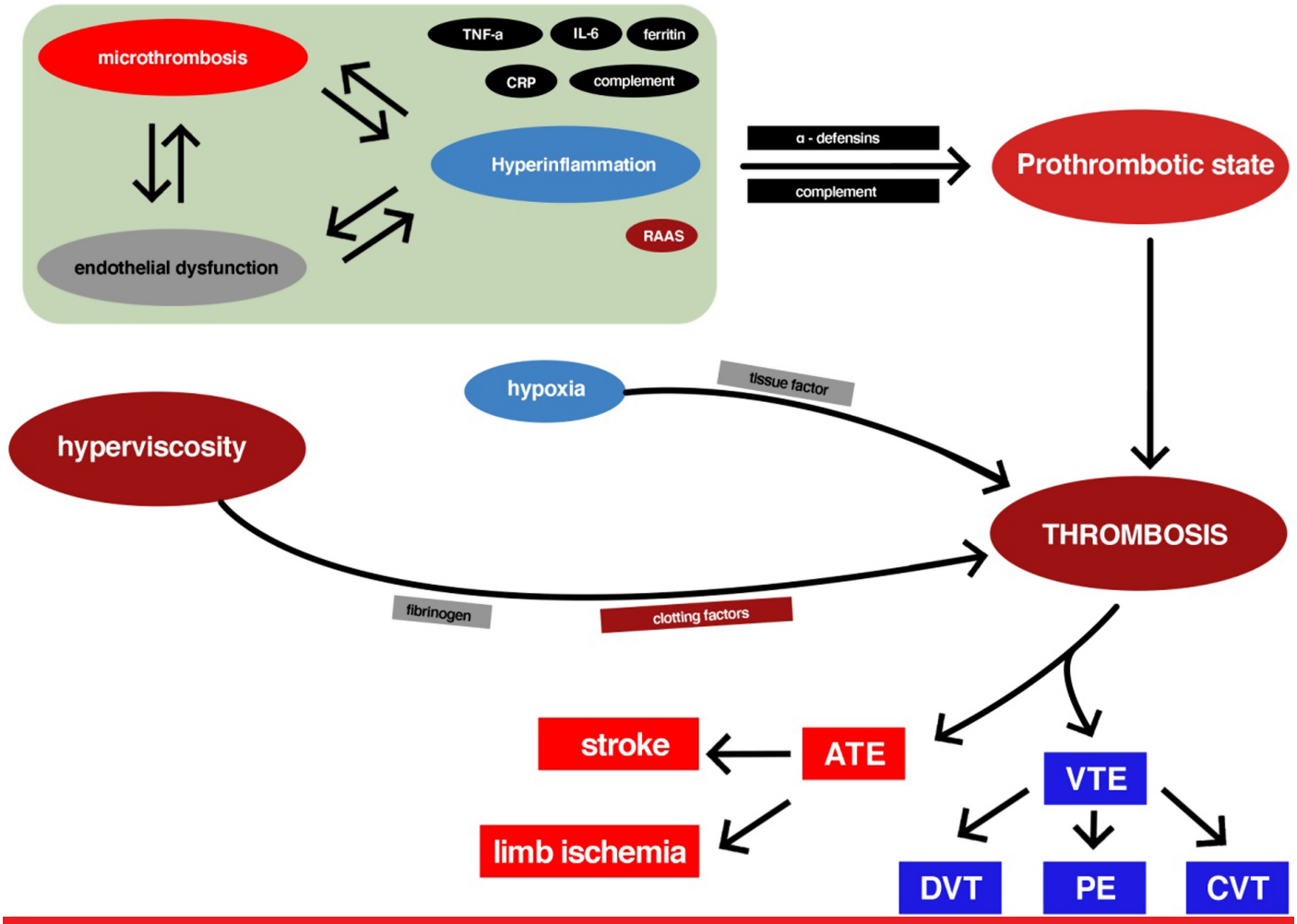

Figure 1. COVID-19-related thrombosis and clinical manifestations.

27% for DVT.[30] Incidence of VTE is increased among critically ill patients. Two meta-analyses with an overall pooled prevalence of 4.8% and 16.7% found 7.6% and 60.8%-85.45% incidence in critically ill patients, respectively.[3,31] In patients using anticoagulants, VTE incidence was lower (23.9% vs. 31.3%) than patients not using anticoagulants before.[32] Median time from admission to VTE diagnosis is found to be 10 days, while the median time from VTE to discharge is 9 days.[14] Venous thromboembolism is described to lead to increased need for mechanical ventilation, ICU admission, and death.[12,14] The most common location is the lower limb, followed by the upper limb and inferior vena cava (IVC).[31] Central venous thrombosis (CVT) is diagnosed approximately 7 days after the establishment of COVID-19 diagnosis, is not related to other medical condition in most cases (57%), and leads to 45.5% mortality.[33] Arterial thromboembolism can occur as peripheral arterial ischemic disease with pain, paresthesia and gangrene, acute coronary syndrome, line-associated radial arterial thrombosis, or ischemic stroke.[2,3,21] The most usual location is the lower limb, followed by the upper limb and aortic thrombosis.[34] Critically ill patients are in greater risk as 2.8% overall prevalence among COVID-19 patients increases to 5.6% in critically ill[3] and 12% in ICU patients.[19] Arterial thromboembolism is related to poor outcomes as amputation ranges from 4% to 11.8% and mortality ranged from 30.1% to 35.3%.[18,21,34] COVID-19-related CVT and ischemic stroke can lead to intracranial hemorrhage.[35] Eventually, central retinal vein occlusion can occur in COVID-19 patients, without any other traditional risk factors[23] (Figure 1).

Medication

Based on the pathophysiology and the studies reporting excess thrombotic risk in patients with COVID-19, research has been trying to identify the role of anticoagulants in the management of the disease.[36] Most of the research and latest guidelines suggest using anticoagulation in hospitalized COVID-19 patients.[15] Tang et al[37] in a retrospective cohort study provided the first evidence that COVID patients with sepsis-induced coagulopathy score higher than 4 or markedly elevated D-dimer levels appeared to have improved mortality when they were treated with anticoagulation (UFH or LMWH) compared to patients receiving no anticoagulation.[38,39] Indeed, since then, many studies have been conducted, mainly observational cohort studies and meta-analyses, since thromboprophylaxis is considered the standard of care and the applicability of these studies is difficult.[38] A retrospective observational study showed that in-hospital mortality was lower in patients receiving

anticoagulation (prophylactic or treatment dose), mostly LMWH.[40] According to a recent meta-analysis, anticoagulation reduces mortality and improves survival compared to no anticoagulation.[41] These findings come in alignment with other available meta-analyses.[6,39] The effect of anticoagulation in thrombotic events (PE, DVT), major bleeding, and adverse events also have been studied but not to a great extent. A meta-analysis showed no increased risk of bleeding events with anticoagulation administration.[42] In contrast, a recent meta-analysis thought the data were limited, and due to poor quality, no conclusion could be derived for the effect of anticoagulation in thrombotic events when compared to no anticoagulation.[6] In contrast to the studies mentioned above, meta-analyses demonstrated that prophylaxis with heparin failed to improve mortality compared to no anticoagulation.[29,43] However, the included studies were limited in sample size or the results were not statistically significant.[29,42,44] The proposed mechanism for the benefit of anticoagulation is by suppressing prothrombotic coagulopathy, therefore preventing thrombosis.[1] More specifically, though, it appears that heparins, apart from being antithrombotic, also have anti-inflammatory and possibly antiviral properties by directly interacting with the s1 spike protein of SARS-CoV-19 and block viral attachment and cell entry.[6,36,39,40,45-47] It has been speculated that heparins can affect proinflammatory cytokines by inhibiting neutrophil chemotaxis and leukocyte immigration, causing decreased inflammation.[40,43] Therefore, heparinoids, primarily LMWH, have been used in critical and noncritical COVID-19 patients. It is possible that therapeutic-dose heparin cannot influence the cascade of inflammation, thrombosis, and organ injury in patients with advanced disease.[36] Research studies have not fully explored the timing of initiation of anticoagulation medication in relation to the degree of severity of the illness from inflammation and coagulation.[36,45,46] Other anticoagulants, besides heparinoids, that have been used in COVID-19 patients are vitamin K antagonists, direct oral anticoagulants (DOACs), and nonoral direct anticoagulants (NOACs).[6,39,41,45] Rivaroxaban has better distribution than heparin, allowing for better access to lung tissue. However, it does not share the other properties of heparin.[46] It is unknown whether there are clinical differences between using rivaroxaban and heparin for COVID-19 patients.[46] Limited studies are comparing the types of anticoagulation and their efficacy in COVID-19. A randomized controlled trial (RCT) directly compared the efficacy between rivaroxaban and enoxaparin in patients with mild to moderate COVID-19. It showed that rivaroxaban had improved efficacy since the group receiving the rivaroxaban had decreased thrombotic events. However, the patient number was small.[48] Billett et al[49], investigating the efficacy of 3 types of anticoagulant drugs (i.e., apixaban, enoxaparin, and UFH) on in-hospital mortality in COVID-19 hospitalized patients, observed that apixaban and enoxaparin had similar beneficial effects on that outcome.[39] Nevertheless, oral anticoagulation (OAC) should be switched to parenteral heparin whenever possible. Vitamin K antagonists and DOACs should be avoided due to possible drug interactions with the antivirals and antibacterial medications used in COVID-19 patients that could change the effect of the anticoagulant.[28,50] If a VTE is identified in a COVID-19 patient, management should change to parenteral therapeutic anticoagulation.[16,41,44] Also, anticoagulation has been used for the treatment of acute limb ischemia, mostly UFH and LMWH, but also DOAC, alone or in combination with other types of therapy.[18,34] Central retinal vein occlusion secondary to COVID-19 has also been treated with anticoagulants, starting on LMWH, which was switched to rivaroxaban, with a favorable outcome.[23] Cerebral venous sinus thrombosis treated with UFH and LMWH was complicated with intracranial hemorrhage, reporting a high prevalence of that complication and mortality.[51] Our understanding of the pathophysiology and the potential role of platelets in the pathogenesis of SARS-CoV-2 infection triggered researchers to investigate the role of antiplatelets in COVID-19. Indeed, aspirin and other antiplatelets have been studied as a potential treatment for COVID-19.[8,52] In a large retrospective study of hospitalized patients, results showed improvement in mortality with the use of in-hospital aspirin compared to no aspirin.[8] However, this observational study comes in contradiction with published randomized control studies. In the RECOVERY trial, outcomes for 28-day mortality and progression to mechanical ventilation were relatively consistent between hospitalized patient who received aspirin and the group that did not. Aspirin was associated with a small reduction of thrombosis, but at the same time with an increased risk of bleeding. On top of that another trial that looked into critically ill patients treated with aspirin did not show improvement in the number of organ support-free days within 21 days.[52] Studies have also tried to investigate the combination of therapeutic heparin with P2Y12 inhibitors, mainly clopidogrel and ticagrelor. However, it was found that the addition of P2Y12 inhibitors in the therapeutic regime does not result in an increase in organ support-free days among noncritically COVID-19 patients.[53] Therefore, initiation of antiplatelets for COVID-19 is not recommended, but future studies will give us better insight shortly (Table 1).

Optimal Dosage

The dosage of anticoagulation has also been the object of extended investigation. Many studies have compared standard prophylactic doses with intermediate and therapeutic doses, in terms of mortality, ATE, VTE, bleeding risk, length of stay (LOS), risk of ICU admission, mechanical ventilation duration, and impact on PO2/FIO2 (P/F) score. Most of the studies and meta-analyses that examined mortality, in-hospital mortality, incidence of death, or all-cause death agree that therapeutic dose does not significantly reduce the risk.[4,7,5,54-60] Intermediate dose did not also achieve to decrease mortality among hospitalized and nonhospitalized COVID-19 patients nor among critically ill patients.[7,61,62] The same results were demonstrated by a meta-analysis that compared intensified (intermediate or therapeutic) anticoagulation with prophylactic anticoagulation.[9] One RCT described a reduction in all-cause death with therapeutic anticoagulation (1.8%) compared to prophylactic dose (7.6%),[63] and another RCT comprehended that intermediate dose can decrease in-hospital death.[8] A meta-analysis resulted in 42% mortality reduction with prophylactic versus

Table 1. Main Studies of Medications Used for COVID-19 Coagulopathy

Title	Author	Research Type	Intervention	Main Results
Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: a propensity score-matched analysis.[8]	Meizlish ML et al	Observational Study	Aspirin vs. no anti-PLT therapy	Aspirin-reduced in-hospital mortality
Heparin in COVID-19 patients is associated with reduced in-hospital mortality: the multicenter Italian CORIST study[41]	Di Castelnuovo A et al	Observational study	Heparin (LMWH/UFH) vs no anticoagulant	Heparin-reduced mortality
Oral rivaroxaban in the prophylaxis of COVID-19-induced coagulopathy[50]	Dhiraj Kumar et al	RCT	Rivaroxaban vs. enoxaparin	Rivaroxaban group had less bleeding and thrombotic episodes
Effect of P2Y12 inhibitors on survival free of organ support among noncritically Ill hospitalized patients with COVID-19: a randomized clinical trial[53]	Jeffrey S Berger et al	RCT	P2Y12 inhibitor plus therapeutic heparin vs. therapeutic heparin in noncritically ill patients	The addition of P2Y12 inhibitor did not significantly affected organ support-free days, mortality, and bleeding events
Effect of antiplatelet therapy on survival and organ support—free days in critically Ill patients with COVID-19[54]	Charlotte A Bradbury et al	RCT	Aspirin vs P2Y12 inhibitor vs. no anti-PLT therapy in noncritically ill patients	Aspirin or P2Y12 inhibitor addition to standard of care did not significantly affected organ support-free days, mortality, and bleeding events

therapeutic dose,[64] and another meta-analysis resulted in 60% higher mortality with intensified dose versus prophylactic dose.[65] Arterial thromboembolism is also demonstrated not to be significantly altered by therapeutic or intermediate dose compared to prophylactic dose.[54,55,58,63,66] Concerning VTE, there is a conflict in literature about the effect of therapeutic or intensified dose compared to prophylactic anticoagulation. Therapeutic anticoagulation seems to outclass prophylactic in preventing VTE among COVID-19 patients,[44,54,57,58,67] despite some RCTs resulting in no significant difference.[55,63] When intermediate dose is involved, the ascendance of intensified dose is not clear. Two meta-analyses found no significant difference,[7,62] while another demonstrated that intensified dose reduces VTE risk to 2.8% versus 5.4% with prophylactic dose), due to a lower PE incidence.[9] Bleeding risk seems to be higher in therapeutic dose compared to prophylactic dose.[5,7,54,56,58,66] In an RCT by Spyropoulos et al[54] major bleeding occur in 4.7% of COVID-19 patients receiving a therapeutic dose of anticoagulation versus 1.6% of those receiving prophylactic dose. Prophylactic dose had also better bleeding profile compared to intensified anticoagulation,[9,65] and intermediate dose.[62] There are 2 meta-analyses, one comparing prophylactic to therapeutic dose and one comparing prophylactic to intermediate dose that found no significant difference in major bleeding.[7,57] In a meta-analysis, LOS is estimated lower for patients receiving prophylactic dose compared to those receiving therapeutic dose.[5] Two RCTs found no significant difference between prophylactic and therapeutic dose at reducing ICU admission and mechanical ventilation duration,[55,63] but another RCT demonstrated that therapeutic dose improved weaning and P/F score over time[59] (Table 2).

Outpatient Use

We found only 3 articles about outpatient use of anticoagulants in patients with COVID-19 infection. A systematic review with meta-analysis by Zeng et al[10] described that outpatient use of oral anticoagulants did not decrease mortality and ICU admission. Analyzed studies include outpatient and hospitalized patients who received OAC before admission. Among analyzed studies, clinicians either continued OAC or switched to subcutaneous LMWH. None of the studies described an improved outcome.[10] Outpatient use of enoxaparin has been examinedin patients with symptomatic COVID-19, in terms of improving hospitalization rate or 30-day all-cause mortality, in two RCTs. In one of them, enoxaparin was administered for 13 days and in the other for 21 days. None of those 2 described an improved outcome.[68,69]

Post-hospitalization Use

There are limited available data regarding the best approach to an anticoagulation strategy post-hospitalization with COVID-19 infection. There is a widespread hypothesis that the risk of hospital-associated VTE may remain after discharge, also for patients with COVID-19.[70] MICHELLE trial is an open-label, multicenter randomized study conducted in Brazil and tried to investigate anticoagulation management in post-hospitalized patients with COVID-19. In this study, patients with a high risk for VTE after discharge, as determined by an IMPROVE score higher than four or score 2-3 plus increased D-dimmers, were prescribed a prophylactic dose of rivaroxaban (10 mg per day) for 35 days. Results showcased that patients who appeared to have an increased risk of thromboembolism (based on an IMPROVE score) had reduced thrombotic events after receiving rivaroxaban 10 mg daily for 35 days, compared to no post-discharge anticoagulation. At the same time, there was no increase in bleeding complications compared to the control group.[67] In addition, a prospective observational single-center study demonstrated that patients with a low risk of VTE post-discharge showed a low incidence of post-discharge VTE, whereas a small group of patients with high-risk VTE who

Table 2. Main RCTs for Optimal Dosage of Anticoagulation

Title	Author	Research Type	Results Summary
Efficacy of different anticoagulant doses for patients with COVID-19: a systematic review and network meta-analysis[57]	Hideto Yasuda et al	RCT	I > P (M)
Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial[54]	Alex C Spyropoulos et al	RCT	P = T (M) P > T (B) P > T (LOS)
Therapeutic versus prophylactic bemiparin in hospitalized patients with nonsevere COVID-19 pneumonia (BEMICOP Study): an open-label, multicenter, randomized, controlled trial[55]	María Marcos-Jubilar et al	RCT	P = T (M, ICUA, ATE, VTE, B)
Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial (HESACOVID)[59]	Lemos ACB et al	RCT	T > P (PFI) T = P (M)
Anticoagulation treatment for patients with coronavirus disease 2019 (COVID-19) and its clinical effectiveness in 2020: a meta-analysis study[60]	Jingyi Ge et al	RCT	I = P (M, ATE, VTE)
Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 admitted to hospital: RAPID randomised clinical trial[63]	Michelle Sholzberg et al	RCT	T > P (M) T = P (ICUA, ATE, VTE)

ATE, arterial thromboembolism; B, bleeding; I, intermediate dose; ICUA, ICU admission; LOS, length of stay; M, mortality; P, prophylactic dose; PFI, P/F ratio improvement; RCTs, randomized clinical trials; T, therapeutic dose; VTE, venous thromboembolism.

were prescribed thromboprophylaxis with prophylactic dose of enoxaparin was also associated with a low incidence of VTE. No bleeding complications occurred in the patients receiving anticoagulation. According to this study, routine prescription post-discharge may not be needed, d with the exception of patients with a high-risk profile.[71] These results appear to come in alliance with the MICHELLE trial. Finally, in a large prospective registry (CORE-19), patients receiving post-discharge anticoagulation had a 46% reduction in post-discharge major thromboembolic events and mortality.[70] Currently, there is no consensus concerning the optimal anticoagulation discharge plan for COVID-19 patients, without documented VTE. However, high-risk individuals may benefit from post-discharge thromboprophylaxis. Future research could give us more answers to identify the appropriate management and the benefits of anticoagulation post-discharge.[41]

CONCLUSION

As a result of COVID-19 hypercoagulability state and increased risk of thrombotic events, anticoagulation seems to be in favor of COVID-19 patients.[36] In-hospital use is already established, but further investigation is needed to clarify the specific groups that will benefit from higher doses, the post-hospitalization strategy, and the groups that may benefit from outpatient anticoagulation treatment.

Availability of data and materials: Available from the corresponding author upon reasonable request.

Ethics Committee Approval: This is a narrative review which was conducted in line with the Ethics Committee of our university and the Commission on Publication Ethics and the Helsinki Declaration.

Informed Consent: Informed Consent was waived due to the reviewing nature of this literature review, which did not included personal data or any intervention on any patients.

Peer-review: Externally peer-reviewed.

Author Contributions: C.M., J.K., T.P., I.K., C.P., and V.K. searched the literature and wrote the paper, and D.V. wrote, supervised, and edited the paper.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declare that this study had received no financial support.

REFERENCES

1. Sagris D, Florentin M, Tasoudis P, et al. Immunomodulation and reduction of thromboembolic risk in hospitalized COVID-19 patients: systematic review and meta-analysis of randomized trials. *J Clin Med*. 2021;10(22):5366. [CrossRef]
2. Fraiman P, Godeiro Junior C, Moro E, Cavallieri F, Zedde M. COVID-19 and cerebrovascular diseases: a systematic review and perspectives for stroke management. *Front Neurol*. 2020;11:574694. [CrossRef]
3. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;136(4):489-500. [CrossRef]
4. Kamel AM, Sobhy M, Magdy N, Sabry N, Farid S. Anticoagulation outcomes in hospitalized Covid-19 patients: a systematic review and meta-analysis of case-control and cohort studies. *Rev Med Virol*. 2021;31(3):e2180. [CrossRef]
5. Giossi R, Menichelli D, Pani A, et al. A systematic review and a meta-analysis comparing prophylactic and therapeutic low molecular weight heparins for mortality reduction in 32,688 COVID-19 patients. *Front Pharmacol*. 2021;12:698008. [CrossRef]
6. Flumignan RL, Tinôco JDS, Pascoal PI, et al. Prophylactic anticoagulants for people hospitalised with COVID-19. *Cochrane Database Syst Rev*. 2020;10(10):CD013739. [CrossRef]
7. Batista DR, Floriano I, Silvinato A, et al. Use of anticoagulants in patients with COVID-19: a living systematic review and meta-analysis. *J Bras Pneumol*. 2022;48(4):e20220041. [CrossRef]
8. Meizlish ML, Goshua G, Liu Y, et al. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: a

propensity score-matched analysis. *Am J Hematol*. 2021;96(4): 471-479. [CrossRef]
9. Wills NK, Nair N, Patel K, et al. Efficacy and safety of intensified versus standard prophylactic anticoagulation therapy in patients with Covid-19: a systematic review and meta-analysis. *medRxiv*. 2022. [CrossRef]
10. Zeng J, Liu F, Wang Y, et al. The effect of previous oral anticoagulant use on clinical outcomes in COVID-19: a systematic review and meta-analysis. *Am J Emerg Med*. 2022;54:107-110. [CrossRef]
11. Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2022; 399(10319):50-59. [CrossRef]
12. Gómez CA, Sun CK, Tsai IT, et al. Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):16025. [CrossRef]
13. Birocchi S, Manzoni M, Podda GM, Casazza G, Cattaneo M. High rates of pulmonary artery occlusions in COVID-19. A meta-analysis. *Eur J Clin Invest*. 2021;51(1):e13433. [CrossRef]
14. Fernández-Capitán C, Barba R, Díaz-Pedroche MDC, et al. Presenting characteristics, treatment patterns, and outcomes among patients with venous thromboembolism during hospitalization for COVID-19. *Semin Thromb Hemost*. 2021;47(4): 351-361. [CrossRef]
15. Fontana P, Casini A, Robert-Ebadi H, Glauser F, Righini M, Blondon M. Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines. *Swiss Med Wkly*. 2020;150:w20301. [CrossRef]
16. Tomerak S, Khan S, Almasri M, et al. Systemic inflammation in COVID-19 patients may induce various types of venous and arterial thrombosis: a systematic review. *Scand J Immunol*. 2021;94(5):e13097. [CrossRef]
17. Fahmy OH, Daas FM, Salunkhe V, et al. Is microthrombosis the main pathology in coronavirus disease 2019 severity?-A systematic review of the postmortem pathologic findings. *Crit Care Explor*. 2021;3(5):e0427. [CrossRef]
18. Putko RM, Bedrin MD, Clark DM, Piscoya AS, Dunn JC, Nesti LJ. SARS-CoV-2 and limb ischemia: a systematic review. *J Clin Orthop Trauma*. 2021;12(1):194-199. [CrossRef]
19. Jenner WJ, Kanji R, Mirsadraee S, et al. Thrombotic complications in 2928 patients with COVID-19 treated in intensive care: a systematic review. *J Thromb Thrombolysis*. 2021;51(3):595-607. [CrossRef]
20. Nossent EJ, Schuurman AR, Reijnders TDY, et al. Pulmonary procoagulant and innate immune responses in critically ill COVID-19 patients. *Front Immunol*. 2021;12:664209. [CrossRef]
21. Rastogi A, Dogra H, Jude EB. COVID-19 and peripheral arterial complications in people with diabetes and hypertension: a systematic review. *Diabetes Metab Syndr*. 2021;15(5):102204. [CrossRef]
22. Abdeen S, Bdeir K, Abu-Fanne R, et al. Alpha-defensins: risk factor for thrombosis in COVID-19 infection. *Br J Haematol*. 2021;194(1):44-52. [CrossRef]
23. Ullah I, Sohail A, Shah MUFA, et al. Central retinal vein occlusion in patients with COVID-19 infection: a systematic review. *Ann Med Surg (Lond)* 2021;71:102898. [CrossRef]
24. Birkeland K, Zimmer R, Kimchi A, Kedan I. Venous thromboembolism in hospitalized COVID-19 patients: systematic review. *Interact J Med Res*. 2020;9(3):e22768. [CrossRef]
25. Luo HC, You CY, Lu SW, Fu YQ. Characteristics of coagulation alteration in patients with COVID-19. *Ann Hematol*. 2021;100(1):45-52. [CrossRef]
26. Abdeen S, Abu-Fanne R, Bdeir K, et al. Divergent impacts of tocilizumab and colchicine in COVID-19-associated coagulopathy: the role of alpha-defensins. *Br J Haematol*. 2022;196(4):923-927. [CrossRef]
27. Brener MI, Hulke ML, Fukuma N, et al. Clinico-histopathologic and single-nuclei RNA-sequencing insights into cardiac injury and microthrombi in critical COVID-19. *JCI Insight*. 2022;7(2): e154633. [CrossRef]
28. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95(7):834-847. [CrossRef]
29. Lu YF, Pan LY, Zhang WW, et al. A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. *Int J Infect Dis*. 2020;100:34-41. [CrossRef]
30. Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS, Syrigos K. Venous thromboembolism in COVID-19: a systematic review and meta-analysis. *Vasc Med*. 2021;26(4):415-425. [CrossRef]
31. Mazzaccaro D, Giannetta M, Fancoli F, et al. COVID and venous thrombosis: systematic review of literature. *J Cardiovasc Surg (Torino)* 2021;62(6):548-557. [CrossRef]
32. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. *Semin Thromb Hemost*. 2020;46(7):763-771. [CrossRef]
33. Tu TM, Goh C, Tan YK, et al. Cerebral venous thrombosis in patients with COVID-19 infection: a case series and systematic review. *J Stroke Cerebrovasc Dis*. 2020;29(12):105379. [CrossRef]
34. Attisani L, Pucci A, Luoni G, et al. COVID-19 and acute limb ischemia: a systematic review. *J Cardiovasc Surg (Torino)* 2021;62(6):542-547. [CrossRef]
35. Daly SR, Nguyen AV, Zhang Y, Feng D, Huang JH. The relationship between COVID-19 infection and intracranial hemorrhage: a systematic review. *Brain Hemorrhages*. 2021;2(4):141-150. [CrossRef]
36. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med*. 2021; 385(9):777-789. [CrossRef]
37. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020 Apr;18(4): 844-847. [CrossRef]. Epub 2020 Mar 13. PMID: 32073213; PMCID: PMC7166509.
38. Maldonado E, Tao D, Mackey K. Antithrombotic therapies in COVID-19 disease: a systematic review. *J Gen Intern Med*. 2020;35(9):2698-2706. [CrossRef]
39. Parisi R, Costanzo S, Di Castelnuovo A, de Gaetano G, Donati MB, Iacoviello L. Different anticoagulant regimens, mortality, and bleeding in hospitalized patients with COVID-19: a systematic review and an updated meta-analysis. *Semin Thromb Hemost*. 2021;47(4):372-391. [CrossRef]
40. Di Castelnuovo A, Costanzo S, Antinori A, et al. Heparin in COVID-19 patients is associated with reduced in-hospital mortality: the multicenter Italian CORIST study. *Thromb Haemost*. 2021;121(8):1054-1065. [CrossRef]
41. Tunjungputri RN, Tetrasiwi EN, Mulansari NA, Harimurti K, Nelwan EJ. Parenteral and oral anticoagulant treatment for hospitalized and post-discharge COVID-19 patients: a systematic review and meta-analysis. *Acta Med Indones*. 2022;54(2):190-209.
42. Jiang L, Li Y, Du H, Qin Z, Su B. Effect of anticoagulant administration on the mortality of hospitalized patients with COVID-19: an updated systematic review and meta-analysis. *Front Med (Lausanne)* 2021;8:698935. [CrossRef]
43. Abdel-Maboud M, Menshawy A, Elgebaly A, Bahbah EI, El Ashal G, Negida A. Should we consider heparin prophylaxis in

COVID-19 patients? a systematic review and meta-analysis. *J Thromb Thrombolysis*. 2021;51(3):830-832. [CrossRef]
44. McBane RD, Torres Roldan VD, Niven AS, et al. Anticoagulation in COVID-19: a systematic review, meta-analysis, and rapid guidance from Mayo clinic. *Mayo Clin Proc*. 2020;95(11):2467-2486. [CrossRef]
45. Ortega-Paz L, Galli M, Capodanno D, et al. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother*. 2022;8(7):677-686. [CrossRef]
46. Jorda A, Siller-Matula JM, Zeitlinger M, Jilma B, Gelbenegger G. Anticoagulant treatment regimens in patients with Covid-19: a meta-analysis. *Clin Pharmacol Ther*. 2022;111(3):614-623. [CrossRef]
47. Mori H, Ohkawara H, Togawa R, Rikimaru M, Shibata Y, Ikezoe T. Diagnosis and treatment of disseminated intravascular coagulation in COVID-19 patients: a scoping review. *Int J Hematol*. 2021;113(3):320-329. [CrossRef]
48. Kumar D, Kaimaparambil V, Chandralekha S, Lalchandani J. Oral Rivaroxaban in the prophylaxis of COVID-19 induced coagulopathy. *J Assoc Physicians India*. 2022;70(2):11-12.
49. Billett HH, Reyes-Gil M, Szymanski J, et al . Anticoagulation in COVID-19: Effect of Enoxaparin, Heparin, and Apixaban on Mortality. *Thromb Haemost*. 2020 Dec;120(12):1691-1699. doi: [CrossRef]. Epub 2020 Nov 13. PMID: 33186991; PMCID: PMC7869055.
50. Tan SHS, Hong CC, Saha S, Murphy D, Hui JH. Medications in COVID-19 patients: summarizing the current literature from an orthopaedic perspective. *Int Orthop*. 2020;44(8):1599-1603. [CrossRef]
51. Castillo-Perez M, Jerjes-Sanchez C, Castro-Varela A, et al. Differences between surviving and non-surviving venous thromboembolism COVID-19 patients: a systematic review. *Thromb J*. 2021;19(1):101. [CrossRef]
52. REMAP-CAP Writing Committee for the REMAP-CAP Investigators, Bradbury CA, Lawler PR, et al. Effect of antiplatelet therapy on survival and organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2022;327(13):1247-1259. [CrossRef]
53. Berger JS, Kornblith LZ, Gong MN, et al. Effect of P2Y12 inhibitors on survival free of organ support among non-critically ill hospitalized patients with COVID-19: a randomized clinical trial. *JAMA*. 2022;327(3):227-236. [CrossRef]
54. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612-1620. [CrossRef]
55. Marcos-Jubilar M, Carmona-Torre F, Vidal R, et al. Therapeutic versus prophylactic Bemiparin in hospitalized patients with nonsevere COVID-19 Pneumonia (BEMICOP Study): an open-label, multicenter, randomized, controlled trial. *Thromb Haemost*. 2022;122(2):295-299. [CrossRef]
56. Kollias A, Kyriakoulis KG, Trontzas IP, et al. High versus standard intensity of thromboprophylaxis in hospitalized patients with COVID-19: a systematic review and meta-analysis. *J Clin Med*. 2021;10(23):5549. [CrossRef]
57. Yasuda H, Mayumi T, Okano H. Efficacy of different anticoagulant doses for patients with COVID-19: a systematic review and network meta-analysis. *Infection*;50(6):1453-1463. [CrossRef]
58. Duo H, Li Y, Sun Y, et al. Effect of therapeutic versus prophylactic anticoagulation therapy on clinical outcomes in COVID-19 patients: a systematic review with an updated meta-analysis. *Thromb J*. 2022;20(1):47. [CrossRef]
59. Lemos ACB, do Espírito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial (HESACOVID) *Thromb Res*. 2020;196(196):359-366. [CrossRef]
60. Ge J, Ma Y, Wu Z, Jin J, Sun X. Anticoagulation treatment for patients with coronavirus disease 2019 (COVID-19) and its clinical effectiveness in 2020: a meta-analysis study. *Med (Baltim)* 2021;100(47):e27861. [CrossRef]
61. Bikdeli B, Talasaz AH, Rashidi F, et al. Intermediate-Dose versus Standard-Dose Prophylactic Anticoagulation in Patients with COVID-19 Admitted to the Intensive Care Unit: 90-day Results from the INSPIRATION Randomized Trial. *Thromb Haemost*. 2022;122(1):131-141. [CrossRef]
62. Reis S, Popp M, Schmid B, et al. Safety and efficacy of intermediate- and therapeutic-dose anticoagulation for hospitalised patients with COVID-19: a systematic review and meta-analysis. *J Clin Med*. 2021;11(1):57. [CrossRef]
63. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with Covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*. 2021;375:n2400. [CrossRef]
64. Aamir Waheed M, Rashid K, Rajab T, et al. Role of anticoagulation in lowering the mortality in hospitalized Covid-19 patients: meta-analysis of available literature. *Saudi Med J*. 2022;43(6):541-550. [CrossRef]
65. Moonla C, Sosothikul D, Chiasakul T, Rojnuckarin P, Uaprasert N. Anticoagulation and in-hospital mortality from coronavirus disease 2019: a systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2021;27:10760296211008999. [CrossRef]
66. Patell R, Chiasakul T, Bauer E, Zwicker JI. Pharmacologic thromboprophylaxis and thrombosis in hospitalized patients with COVID-19: a pooled analysis. *Thromb Haemost*. 2021;121(1):76-85. [CrossRef]
67. Sridharan GK, Vegunta R, Rokkam VRP, et al. Venous thromboembolism in hospitalized COVID-19 patients. *Am J Ther*. 2020;27(6):e599-e610. [CrossRef]
68. Barco S, Voci D, Held U, et al. Enoxaparin for primary thromboprophylaxis in symptomatic outpatients with COVID-19 (Ovid): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet Haematol*. 2022;9(8):e585-e593. [CrossRef]
69. Cools F, Virdone S, Sawhney J, et al. Thromboprophylactic low-molecular-weight heparin versus standard of care in unvaccinated, at-risk outpatients with COVID-19 (ETHIC): an open-label, multicentre, randomised, controlled, phase 3b trial. *Lancet Haematol*. 2022;9(8):e594-e604. [CrossRef]
70. Zuin M, Engelen MM, Barco S, et al. Incidence of venous thromboembolic events in COVID-19 patients after hospital discharge: a systematic review and meta-analysis. *Thromb Res*. 2022;209:94-98. [CrossRef]
71. Engelen MM, Vandenbriele C, Balthazar T, et al. Venous thromboembolism in patients discharged after COVID-19 hospitalization. *Semin Thromb Hemost*. 2021;47(4):362-371. [CrossRef]