

# The Use of Therapeutic-Dose Anticoagulation and Its Effect on Mortality in Patients With COVID-19: A Systematic Review

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## Abstract

The incidence of venous thromboembolism (VTE) events in patients with COVID-19 treated with a standard thromboprophylaxis dose of anticoagulants remains high. We conducted a systematic review in order to explore the association between therapeutic-dose anticoagulation and its effect on mortality in patients with COVID-19. A systematic search was carried out using the electronic databases of PubMed, EuropePMC, and the Cochrane Central Database, using specific keywords. All articles that fulfilled the inclusion criteria were included in the qualitative analysis. There were 8 observational studies included in the final qualitative analysis. Quality assessment using the Newcastle-Ottawa Scale (NOS) showed a mean score of  $7.5 \pm 1.06$ , indicating moderate to high quality of the studies. Three retrospective cohort studies reported a reduction in the mortality rate, while 6 other studies showed no mortality benefits among patients with COVID-19 treated with therapeutic-dose anticoagulation. There was a slight tendency toward a reduction in the mortality rate among mechanically-ventilated patients with COVID-19 receiving therapeutic-dose anticoagulation. Bleeding events and thrombotic complications among patients receiving therapeutic-dose anticoagulation were reported in 3 studies. Although it is too soon to draw any conclusions, this systematic review draws attention to current evidence regarding the association between therapeutic-dose anticoagulation and its effect on mortality in patients with COVID-19.

## Keywords

therapeutic-dose anticoagulation, anticoagulants, COVID-19, SARS-CoV-2, mortality

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## Introduction

The Coronavirus disease 2019 (COVID-19) pandemic is a global ongoing issue with more than 15 million known cases to date, and a mortality rate of 5.4% worldwide.<sup>1</sup> While COVID-19 is easily contracted, only a minority of patients with particular comorbidities will develop severe COVID-19 with features of hyper-inflammation and complications, including acute respiratory distress syndrome (ARDS), multi-organ failure (MOF), and death.<sup>2-6</sup> Hypothetically, the fate of this relentless pandemic might finally be decided by the discovery of either a vaccine or definite treatment for COVID-19.

Ever since preliminary evidence was released, showing that anticoagulant administration could reduce mortality of patients with severe COVID-19,<sup>7</sup> the issues of thrombosis and coagulopathy have gained special attention in the pathogenesis and treatment of COVID-19. The persistence of a high incidence of venous thromboembolism (VTE) even in patients with COVID-19 treated with a standard thromboprophylaxis dose of anticoagulants raises the question of whether the administration of therapeutic-dose anticoagulants may improve the

prognosis of patients with COVID-19.<sup>8,9</sup> To clarify this, we conducted a systematic review to explore the association between therapeutic-dose anticoagulation and its effect on mortality in patients with COVID-19.

## Methods

### Search Strategy and Study Selection

This systematic review was conducted in compliance with the guidelines for the Preferred Reporting Items for Systematic

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Reviews and Meta-Analyses (PRISMA).<sup>10</sup> A literature search was performed of the electronic databases of PubMed, EuropePMC, and the Cochrane Central Database, with specific search terms (“COVID-19” OR “SARS-CoV-2”) AND (“anticoagulant” OR “anticoagulation” OR “heparin”). A time restriction was applied from 1 December 2019 to 30 June 2020, which was the date of our search finalization. After collecting the results of the initial search, duplicates were removed. Three independent authors (IW, RA, IH) sorted the relevant articles by screening the title and abstracts. Finally, the full texts of all prospective articles were examined for relevance based on the inclusion and exclusion criteria.

### **Inclusion and Exclusion Criteria**

The following characteristics of articles were included in the analysis: research articles in which the subjects were adult COVID-19 patients with available data on the use of therapeutic-dose anticoagulation and the main outcome of interest, which was all-cause mortality among those patients. We broadly defined therapeutic-dose anticoagulation treatment as the use of any therapeutic-range anticoagulation therapies, either unfractionated heparin (UFH), low-molecular weight heparin (LMWH), vitamin K antagonist (VKA), or direct oral anticoagulants (DOAC). Review articles, non-research letters, case reports, commentaries or perspectives, non-English language articles, and those based on pediatric patients (i.e., < 18 years old) were excluded from this study.

### **Data Collection and Quality Assessment**

Data collected from the included studies were extracted by 3 independent authors (IW, RA, IH) using a pre-constructed standardized form, which consisted of author, study design and location, total samples, age, gender, anticoagulation (type & dose), main result/key findings, and Newcastle-Ottawa Scale (NOS) score. Quality assessment of the included studies was carried out independently using the NOS. It is a risk of bias assessment tool for non-randomized studies in systematic review and/ or meta-analyses based on 3 domains: the selection of the study groups; the comparability of the groups; and the ascertainment of exposure and outcome for case-control or cohort studies, respectively.<sup>11</sup> A maximum of 9 points can be assigned for the least risk of bias in those 3 domains. Any disagreements were resolved through discussion.

## **Results**

### **Study Selection and Characteristics**

The initial searches yielded 1,539 records, reduced to 1,441 after the removal of duplicates. After assessing the title/abstract of each paper for data of interest, 1,383 records were excluded. The 58 remaining records were then assessed for eligibility to be included in this systematic review. Thirty-five articles were excluded because they did not report our outcome of interest. Another 15 studies were excluded because they did not report

the use of therapeutic-dose anticoagulation. Ultimately, 8 studies were included in the final qualitative synthesis (Figure 1).<sup>12-20</sup> The main features of the 8 studies are presented in Table 1.

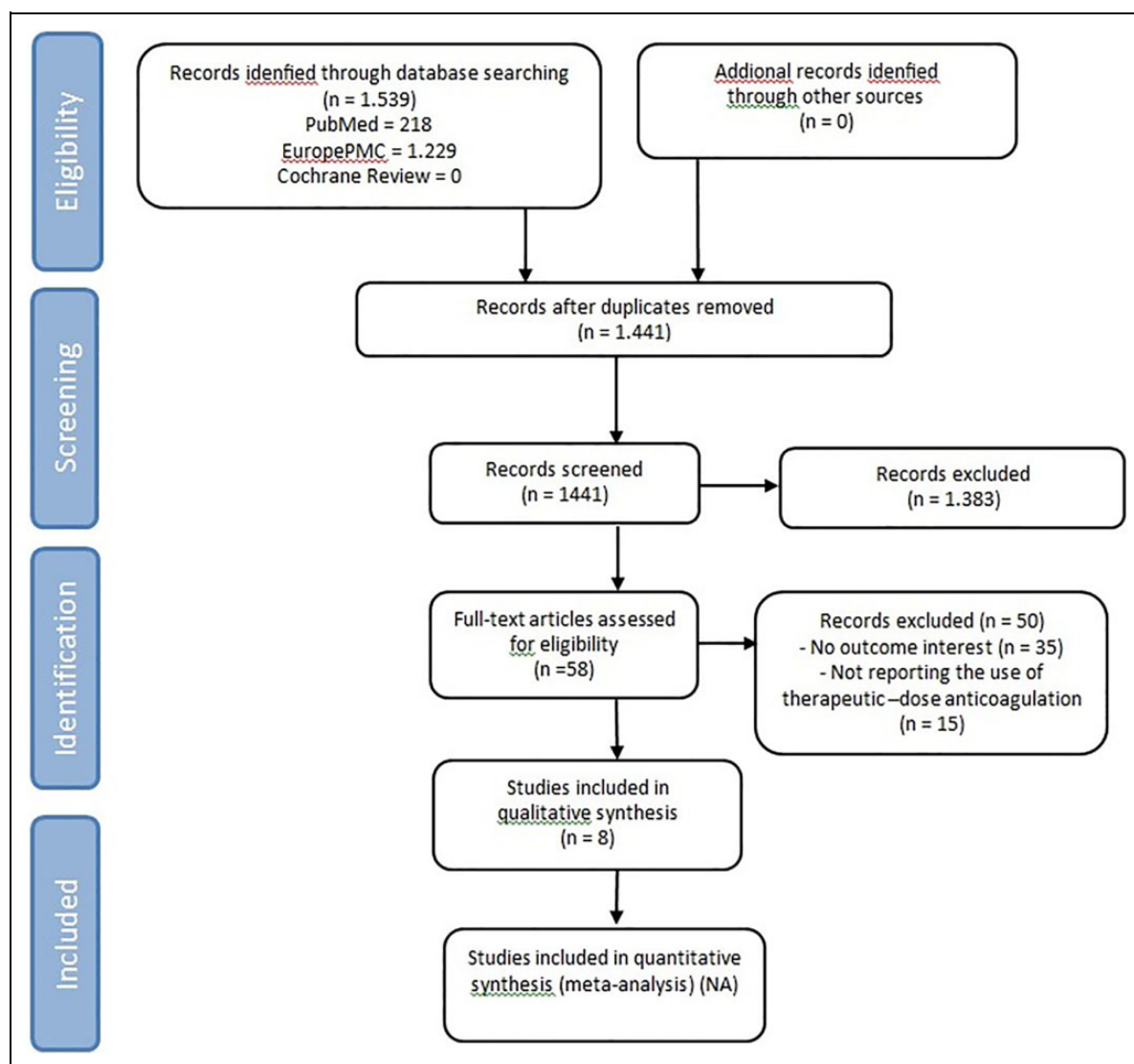
### **Therapeutic-Dose Anticoagulation and Mortality**

Three retrospective cohort studies showed a reduction in the mortality rate of hospitalized patients with COVID-19 treated with therapeutic-dose anticoagulation.<sup>12,13,19</sup> Two studies showed a significant reduction of mortality in mechanically-ventilated patients,<sup>12,13</sup> while Rossi et al. showed a reduction in the mortality rate among elderly patients.<sup>19</sup> Trinh et al. found a 79% reduction in mortality among mechanically-ventilated patients with COVID-19 who were therapeutically anticoagulated for  $\geq 5$  days as compared to those receiving prophylactic anticoagulants in a multivariate Cox proportional hazard regression model (HR 0.209, 95% CI 0.10-0.46),  $P < 0.001$ .<sup>12</sup> Meanwhile, Paranjpe et al. reported comparable in-hospital mortality rates in all hospitalized patients treated with therapeutic-dose anticoagulation as compared to those who did not receive therapeutic-dose anticoagulation (22.5% vs 22.8%).<sup>13</sup> Their subgroup analysis among mechanically-ventilated patients with COVID-19 showed improved mortality in those patients receiving therapeutic-dose anticoagulation (29.1% vs 62.7%). Furthermore, Rossi et al. reported that the use of therapeutic-dose anticoagulation by DOAC administration was associated with lower mortality rate among elderly patients with COVID-19 (adjusted HR 0.38, 95% CI 0.17–0.58).<sup>19</sup>

The remaining 5 studies showed no mortality benefits among patients with COVID-19 receiving therapeutic-dose anticoagulation (Table 1).<sup>14,16-28</sup> The included studies consisted of 1 prospective cohort,<sup>18</sup> and 4 retrospective cohorts.<sup>14,16,17,20</sup> Among these studies, there were 2 studies in which the patients were on pre-admission chronic anticoagulant treatment which was continued during hospitalization.<sup>16,20</sup> A study by Pierce-Williams et al. was the only study conducted among pregnant woman with severe or critical COVID-19 and they found no difference in mortality rate between therapeutically-anticoagulated patients and those receiving prophylactic anticoagulant treatment (all patients survived).<sup>17</sup>

### **Type and Dose of Therapeutic Anticoagulant**

The types and doses of therapeutic anticoagulants used in the included studies were mostly inadequately described (Table 1). In 4 studies, the type of therapeutic anticoagulant used was not specified.<sup>13,16,18,20</sup> The study by Trinh et al. was the only study that clearly defined the doses and types of therapeutic and prophylactic anticoagulants that were used in their research.<sup>12</sup> They defined the therapeutic-dose anticoagulation group as patients receiving UFH (15 u/kg/h or greater with or without a heparin bolus of 80 units/kg with the goal of achieving activated partial thromboplastin time (APTT) of 70–100 seconds), LMWH (1 mg/kg twice daily if the glomerular filtration rate



**Figure 1.** PRISMA guideline.

was  $> 30$  mL/min or once daily if the glomerular filtration rate was  $\leq 30$  mL/min), or DOAC (Apixaban 10 mg twice daily, or 5 mg twice daily in patients who had received prior anticoagulant treatment).<sup>12</sup>

### Bleeding Events

There were 3 studies that reported the bleeding event rate among hospitalized patients with COVID-19 receiving therapeutic-dose anticoagulation.<sup>12,13,20</sup> A significant increase in the rate of bleeding events was reported by Tremblay et al. among those receiving therapeutic anticoagulation as compared to patients not on anticoagulant nor antiplatelet therapy (1.2% vs 0.4%)<sup>20</sup>, while Trinh et al. also showed an increased trend in the bleeding rate, although they reported that this increase in the rate of bleeding complications was not significant (31.7% vs 20.5,  $P = 0.07$ ).<sup>12</sup> Paranjpe et al. reported no bleeding events among those treated with therapeutic-dose

anticoagulation (1.9% vs 3%,  $P = 0.2$ ); nevertheless in its subgroup analysis they found that bleeding events were more common among intubated patients (30 of 395; 7.5%) than non-intubated patients (32 of 2,378; 1.35%).

### Thrombotic Events Among Patients Treated With Therapeutic-Dose Anticoagulants

Thrombotic events among patients treated with therapeutic-dose anticoagulation was reported in 3 of the included studies.<sup>14,16,20</sup> Llitjos et al. reported that the overall rate of peripheral VTE events in their study was 69%.<sup>14</sup> The proportion of peripheral VTE was significantly higher in patients treated with prophylactic-dose anticoagulation compared with patients receiving therapeutic-dose anticoagulation (100% vs 56%,  $P = 0.03$ ). Surprisingly, the incidence of pulmonary embolism (PE) was 33% among patients treated with therapeutic-dose anticoagulation. Moreover, Klok et al. reported that the overall rate of thrombotic complications

Table 1. Characteristics of the Included Studies.

Author	Study design/location	Samples	Age (mean)	Male sex (%)	Anticoagulation	Result/key findings	Potential bias and limitation	NOS
Trinh et al <sup>12</sup>	Retrospective Cohort / USA	244 ICU patients (Mechanically-ventilated patients) TA 65.9% (161/244) vs PA 34.1% (83/244)	TA vs PA (59.7 vs 59.3)	TA vs PA (65.2 vs 67.5)	<b>Definition of TA:</b> - Heparin IV with aPTT goal of 70-100 sec - Enoxaparin 1 mg/kg BID (GFR > 30), 1 mg/kg daily (GFR < 30) SC - Apixaban 10 mg BID, or 5 mg BID (with prior anticoagulation) <b>Definition of PA:</b> - Heparin 5000 U SC BID/TID - Enoxaparin 40 mg daily - Apixaban 2.5 mg, or 5 mg BID (without prior anticoagulation) <b>Type and dose of anticoagulants:</b> not defined	<b>In-hospital mortality:</b> Therapeutic anticoagulation for $\geq 5$ days reduces death rate by 79.1% [(Propensity-weighted HR 0.209; 95% CI 0.10-0.46 (P < 0.0001))] <b>Bleeding Events:</b> TA vs PA (31.7% vs 20.5%, P = 0.07)	- Independent validation of record was not adequate - Possible immortal time bias	8
Paranjpe et al <sup>13</sup>	Retrospective Cohort / USA	2773 patients (395 mechanically-ventilated patients) TA 28% (786/2,773) vs Not TA 72% (1,987/2,773)	NA	NA		<b>Mortality (with median survival days):</b> - In all hospitalized patients: TA vs not TA (22.5%, 21 days vs 22.8%, 14 days) - In mechanically ventilated patients: TA vs not TA (29.1%, 21 days vs 62.7%, 9 days) - Longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day; 95% CI 0.82 to 0.89; P < 0.001) <b>Bleeding Events:</b> - TA vs Not TA (3% vs 1.9%, P = 0.2) - Bleeding events more common among intubated patients	- Independent validation of record was not adequate - Group definition of anticoagulants was unclear - Baseline characteristics were not provided	7
Llitjos et al <sup>14</sup>	Retrospective Cohort / France	26 ICU patients (mechanically-ventilated patients) TA 69% (18/26) vs PA 31% (8/26)	TA vs PA (67.5 vs 68)	TA vs PA (78 vs 75)	<b>Definition of TA:</b> - LMWH or UFH with anti-Xa monitoring, with therapeutic levels of 0.3 to 0.7 U/mL of anti-Xa activity. <b>Definition of PA:</b> not defined	<b>Mortality:</b> TA vs PA (11.1% vs 12.5%) <b>Venous thromboembolic events:</b> - DVT: TA vs PA (56% vs 100%, P = 0.03) - PE: TA vs PA (33% vs 0%) - VTE events still occur even in patients on TA	- Independent validation of record was not adequate - Limited statistical analysis due to small sample size and number of outcomes	7
Klok et al <sup>15,16</sup>	Retrospective Cohort / Netherlands	184 ICU patients TA 9.2% (17/184) vs PA 90.8% (167/184)	Total: 64 (SD 12)	Total: 76	<b>Definition of TA:</b> Prior use of anticoagulants which was continued during hospitalization <b>Definition of PA:</b> Nadroparin 2850—5700 U SC daily/BID	<b>Mortality:</b> - Use of chronic TA was not associated with all-cause death (HR 0.79, 95% CI 0.35–1.8) - Patients with thrombotic complications were at higher risk of all-cause death (HR of 5.4, 95%CI 2.4–12) <b>Thrombotic Complications (Arterial and Venous):</b> - Total Events: 75 (PE65, DVT 1, catheter thromboses 2, ischemic stroke 5, systemic arterial embolism 2) - Chronic TA was associated with a lower risk of the composite outcome (thrombotic complications and death HR 0.29, 95%CI 0.09–0.92)	- Independent validation of records was not adequate - Baseline characteristics and complete data were not adequately provided	6

(continued)

**Table 1. (continued)**

Author	Study design/location	Samples	Age (mean)	Male sex (%)	Anticoagulation	Result/key findings	Potential bias and limitation	NOS
Pierce-Williams et al <sup>17</sup>	Retrospective and Prospective Cohort / USA	64 Pregnant Women [Critical vs Severe (31% vs 69%)] TA 16% (10/64) vs PA 58% (37/64)	Total: 33	Total: 0	<b>Definition TA and PA:</b> was not defined. <b>Type of Anticoagulants:</b> heparin / LMWH	<b>Mortality:</b> 0% in both groups (TA vs PA)	- No outcome of interest (mortality) was observed in either group - Study design was not primarily aimed to investigate the effect of anticoagulants on the outcome	9
Khalil et al <sup>18</sup>	Prospective Cohort / UK	220 patients (38 mechanically-ventilated patients TA 12.3% (27/220) vs PA 79.1% (174/220)	Total: 66.9	Total: 59.1	<b>Definition TA and PA:</b> not defined. <b>Type and dose of anticoagulants:</b> not defined	<b>Mortality:</b> There was no association between the use of TA and mortality (8.6% vs 13.6%, $P = 0.323$ )	- Independent validation of records was not adequate - Study design was not primarily aimed to investigate the effect of anticoagulants on the outcome	8
Rossi et al <sup>19</sup>	Retrospective Cohort / Italy	70 Elderly Patients TA: 37.1% (26/70) vs Not TA: 62.9% (44/70)	Total: 79	Total: 50	<b>Definition of TA:</b> Patients treated with DOAC (Aroxaban 42.3%; Apixaban 34.6%; Edoxaban 15.4% and Dabigartan 7.7%)	<b>Mortality:</b> The use of chronic TA (DOAC) was associated with decreased mortality risk (adjusted HR 0.38; 95% CI 0.17–0.58, $P = 0.01$ )	- Independent validation of records was not adequate - Baseline severity was not provided - Treatment during hospitalization was not described - No description of prophylactic-dose anticoagulant use in the other group	8
Tremblay et al <sup>20</sup>	Retrospective Cohort / USA	3772 patients (13.8% invasive mechanically-ventilated patients) TA 6.4% (241/3772) vs No AC/antiplatelet 75.8% (2859/3772)	TA vs not on TA/ or antiplatelet (73.2 vs 52.36; after propensity-matched: 68.4 vs 69.8)	TA vs not on TA/ or antiplatelet (55.2 vs 53.6; after propensity-matched: 58.3 vs 50.8)	<b>Definition of TA:</b> Patients on prior use of anticoagulants which was continued during hospitalization <b>Type and dose of anticoagulants:</b> not defined	<b>Mortality:</b> There was no significant difference in survival (HR 1.208 (95% CI, 0.750–1.946, $P = 0.367$ ) or time-to mechanical ventilation (HR 0.905, 95% CI 0.571–1.435, $P = 0.742$ ) <b>Major Bleeding events:</b> TA vs No AC/antiplatelet (1.2% vs 0.4% ( $P = 0.007$ ))	- Independent validation of records was not adequate - No description of prophylactic-dose anticoagulant use in the other group	8

TA: Therapeutic-dose anticoagulation; PA: Prophylactic-dose anticoagulation; AC: Anticoagulants; BID: twice daily; TID: thrice daily or 3 times a day; ICU: Intensive Care Unit; NOS: Newcastle-Ottawa Scale; HR: Hazard Ratio; CI: Confidence Interval; aPTT: activated partial thromboplastin time; UFH: Unfractionated Heparin; LMWH: Low-Molecular Weight Heparin; DOAC: Direct Oral Anticoagulant.

in their study sample was 41% with PE accounting for 86.7% of all thrombotic events.<sup>15,16</sup> This specific complication was also found in 17.6% of patients receiving therapeutic-dose anticoagulation. Nevertheless, Tremblay et al. reported no significant difference in thrombotic events among patients treated with therapeutic-dose anticoagulant compared to those not receiving anticoagulants and or/antiplatelet therapy (1.2% vs 1.0%,  $P = 0.076$ ).<sup>20</sup>

### Quality Assessment and Risk of Bias

Quality assessment using NOS showed mean score of  $7.5 \pm 1.06$  indicating moderate to high quality of studies. The risk of bias was mostly due to methodological limitation, which consisted of inadequate data validator/investigator (outcome and/or exposure), incomplete data reporting (reporting bias), and unspecified definition of the type and dose of anticoagulants (e.g. therapeutic-dose and prophylactic-dose). Overall, the included studies were of small sample size with very low number of events/exposures; thus the adjusted analysis might cause overfitting model.

### Discussion

Preliminary evidence of improved survival among patients with severe COVID-19 receiving anticoagulants,<sup>7</sup> along with the initial pathologic findings of microvascular thrombosis in pulmonary small vessels in critically-ill COVID-19 patients,<sup>21</sup> have shifted researchers' attention to the role of coagulopathy and thrombosis in the pathogenesis and treatment of COVID-19.<sup>22</sup> The present concept of a unique hypercoagulable state in SARS-CoV-2 infection, commonly known as COVID-19-associated coagulopathy (CAC),<sup>23</sup> centers around the bidirectional model of thrombosis and inflammation,<sup>24,25</sup> which may be recognized as a specific condition called thromboinflammation.<sup>26</sup> The initial inflammatory response originates in the alveoli when SARS-CoV-2 invades host cells through the angiotensin-converting enzyme 2 (ACE2).<sup>27,28</sup> The disruption of both epithelial and endothelial cells leads to the release of inflammatory cytokines along with endothelial activation and dysfunction, expression of tissue factor (TF), platelet activation, increased levels of von Willebrand factor (VWF) and Factor VIII (FVIII), which subsequently contribute to thrombin formation and fibrin clot deposition.<sup>24</sup> Furthermore, thrombin promotes inflammation through platelet activation from neutrophil-extracellular trap (NET) and monocyte activation through protease-activated receptor (PAR) signaling.<sup>24,26</sup> This bidirectional model is further aggravated in the presence of hypoxia.<sup>29</sup> Hypoxia causes vasoconstriction of small pulmonary vessels, further promoting endothelial dysfunction.<sup>27</sup> Hypoxia also causes a prothrombotic state of the endothelium through the alteration of transcriptional factors, including growth response gene 1 (Egr1) and hypoxia-inducible factor 1 (HIF-1).<sup>30,31</sup>

Therapeutic-dose anticoagulation strategy commonly refers to the use of anticoagulants in patients with proven VTE

events,<sup>32</sup> while prophylactic-dose anticoagulation denotes anticoagulants that are given to prevent VTE events among hospitalized patients at high risk of thrombosis. Due to the nature of the hypercoagulable state in patients with COVID-19, the use of prophylactic-dose anticoagulation is recommended for all hospitalized COVID-19 patients to reduce the risk of a VTE event.<sup>33,34</sup> While this recommendation is still endorsed by most guidelines around the globe (Table 2), an emerging interest has arisen toward higher-dose thromboprophylaxis or therapeutic-dose anticoagulation among patients with COVID-19. This is mostly due to the high incidence of VTE events despite the use of standard prophylactic-dose therapy among patients with COVID-19.<sup>14</sup>

This systematic review was conducted to address the current interest in the use of therapeutic-dose anticoagulation in patients with COVID-19. We have highlighted some current evidence on the association of therapeutic-dose anticoagulation with mortality among hospitalized patients with COVID-19.

There was a slight trend in the evidence toward a reduction of mortality rate among mechanically-ventilated patients with COVID-19 receiving therapeutic-dose anticoagulation therapy in comparison to those treated with standard prophylactic-dose anticoagulation therapy. It seems the explanation of this phenomenon relies on the characteristics of the hypercoagulable state in critically ill patients, since the benefit was mostly not observed in hospitalized patients with COVID-19 in other settings. Critical illness is a well-known risk factor for thrombosis due to prolonged immobilization, invasive lines and devices (e.g. central venous access), the use of vasopressors and other medications, blood product transfusion, mechanical ventilation, and certain acquired thrombophilias.<sup>41,42</sup>

While this glimpse of evidence may partially support the use of therapeutic-dose anticoagulants in patients with these specific conditions,<sup>12,13</sup> 2 main factors must be taken into consideration before implementing such treatment in clinical practice. Firstly, it is possible that only particular subgroups of critically-ill patients with certain risk factors could benefit from therapeutic-dose anticoagulation, as Klok et al. reported no mortality benefits among those receiving therapeutic-dose anticoagulation.<sup>16</sup> Secondly, the bleeding risk among those patients must be evaluated carefully before using therapeutic-dose anticoagulation. While only 1 study showed a statistically-significant increase in the bleeding risk among patients treated with therapeutic-dose anticoagulation,<sup>20</sup> 2 other studies also showed an increase among those receiving this treatment, although this was not significant.<sup>12,13</sup> A larger sample size in the study could have led to a statistically-significant result. Therefore, we propose that the use of therapeutic-dose anticoagulation must be further elucidated in the settings of larger propensity-matched prospective cohorts or randomized controlled trials before its implementation in clinical practice. Currently, as of 15th August 2020, a total of 20 clinical trials have been registered in the National Institutes of Health (<https://www.clinicaltrials.gov/>) in order to evaluate the efficacy of therapeutic-dose anticoagulation in patients with COVID-19.

**Table 2.** Current Guideline Recommendations for Therapeutic-Dose Anticoagulation in COVID-19.

Guideline	Recommendation	Last updated
<b>NIH</b> <sup>35</sup>	Therapeutic doses of anticoagulant in patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19 in patients who are admitted to a hospital	June 25, 2020
<b>ACCP</b> <sup>36</sup>	In patients with COVID-19 and recurrent VTE despite anticoagulation with therapeutic weight-adjusted LMWH (and documented compliance), we suggest increasing the dose of LMWH by 25% to 30%. In patients with COVID-19 and recurrent VTE despite anticoagulation with apixaban, dabigatran, rivaroxaban or edoxaban (and documented compliance), or VKA (in the therapeutic range) we suggest switching treatment to therapeutic weight-adjusted LMWH.	June 23, 2020
<b>GIHP and GFHT</b> <sup>37</sup>	In case of very high thrombotic risk, it is proposed to prescribe therapeutic doses of LMWH, e.g. enoxaparin, 100 IU/kg/12 h SC, or in case of severe renal insufficiency of UFH, 500 IU/kg/24 h, IV after a bolus of 5000 IU, and with dosage adjustment according to anti-Xa activity. The use of ECMO exposes the patient to a very high risk of thrombosis. In this setting, we propose therapeutic anticoagulation with UFH as soon as ECMO is initiated (independently of the ECMO flow rate), with a target anti-Xa level between 0.5 and 0.7 IU/mL. In case of an increased inflammatory syndrome (e.g., fibrinogen > 8 g/L or 800 mg/dL) and/or a rapid increase in D-dimer concentration to > 3 µg/mL (3000 ng/mL), it is suggested that the administration of therapeutic doses of heparin be considered even in the absence of clinical thrombosis, taking into account the risk of hemorrhage.	June 19, 2020
<b>BSTH and ABHH</b> <sup>38</sup>	The use of therapeutic-doses of anticoagulation should be restricted to treatment of confirmed VTE events No evidence to date supporting the increase of the dose of pharmacologic thromboprophylaxis to intermediate, nor therapeutic doses.	June 3, 2020
<b>WHO</b> <sup>39</sup>	No specific comment on therapeutic-dose anticoagulation	May 27, 2020
<b>ISTH</b> <sup>40</sup>	change of anticoagulant regimen (i.e., from prophylactic or intermediate-dose to treatment-dose regimen) can be considered in patients without established VTE but deteriorating pulmonary status or ARDS (50% of respondents) Treatment-dose heparin should not be considered for primary prevention until the results of RCT are available. A change of anticoagulant regimen (i.e., from prophylactic or intermediate-dose to treatment-dose regimen) can be considered in patients without established VTE but deteriorating pulmonary status or ARDS	May 27, 2020
<b>SISET</b> <sup>43</sup>	The use of therapeutic doses of UFH or LMWH, outside of established diagnoses of VTE or as a bridging strategy in patients on VKA is currently not supported by evidence and cannot be recommended as a standard treatment for all COVID-19 patients.	March 4, 2020

NIH: National Institutes of Health; ACCP: American College of Chest Physician; GIHP: The French Working Group on Perioperative Hemostasis; GFHT: the French Study Group on Thrombosis and Hemostasis; SISET: The Haemostasis Italian Society on Thrombosis and Haemostasis; BSTH: Brazilian Society of Thrombosis and Hemostasis (BSTH); ABHH: the Thrombosis and Hemostasis Committee of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy; WHO: World Health Organization, International Society of Thrombosis and Haemostasis (ISTH). RCT: Randomized Controlled Trial; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; VTE: Venous Thromboembolism; ECMO: Extracorporeal membrane oxygenation; UFH: Unfractionated Heparin; LMWH: Low-Molecular Weight Heparin; VKA: Vitamin K Antagonists;

While the type of therapeutic anticoagulant was not described in 4 included studies, heparin-based anticoagulants (UFH and LMWH) were the most frequent type of anticoagulants reported in the other studies. These findings may reflect current supposition among physicians that heparin may have therapeutic effect in COVID-19 beyond its anticoagulant properties. Heparin is postulated to wield both antiviral and anti-inflammatory effects through inhibition of viral entry and dampening of pro-inflammatory signals, respectively.<sup>43</sup> Even though these theoretical hypotheses are biologically plausible, it still lacks strong evidence in supporting these effects. Furthermore, whether heparin-based anticoagulants are superior to DOAC or VKA in terms of clinical outcome in patients with COVID-19 requires further study.

There were several limitations to this systematic review. Most of the studies included in our analysis were observational and retrospective in nature, thus the strength of the association

could not be accurately measured. As we pointed out earlier, the moderate risk of bias of the included studies were mostly from reporting bias due to incomplete data reporting and unspecified definition of anticoagulants (e.g. therapeutic-dose and prophylactic-dose). These issues may translate into uncertain effect estimates of these individual studies. We also included an unpublished study which was not yet peer-reviewed. Due to the rapid nature of publication of new studies in this pandemic era, it is more than possible that newly-relevant and potential studies may have been published since the end date of our search finalization.

### *Implications for Clinical Practice*

This systematic review showed a slight trend of small evidence that therapeutic-dose anticoagulation may improve survival among critically-ill patients with COVID-19. This new

evidence does not justify alteration of the existing guidelines (Table 2). It is still insufficient to recommend or against the therapeutic-dose anticoagulation among critically-ill hospitalized patients with COVID-19 in the absence confirmed VTE (DVT or PE) event.<sup>9,44</sup> Therefore, until further evidence from randomized clinical trials, we only suggest using therapeutic-dose anticoagulation among COVID-19 patients with imaging-confirmed VTE or at least in highly suspected patients when imaging are inaccessible.

## Conclusion

We have highlighted some current evidence on the association of therapeutic-dose anticoagulation with mortality in patients with COVID-19. Prospective cohorts and or randomized controlled trials are desperately needed in exploring the definitive effects of therapeutic-dose anticoagulants in hospitalized patients with COVID-19.

## Authors' Note

The data used to support the findings of this study are included within the article. Ethics and Informed consent were not applicable for this systematic review.


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