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Different Anticoagulant Regimens, Mortality, and Bleeding in Hospitalized Patients with COVID-19: A Systematic Review and an Updated Meta-Analysis

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Abstract

We conducted a systematic review and a meta-analysis to assess the association of anticoagulants and their dosage with in-hospital all-cause mortality in COVID-19 patients. Articles were retrieved until January 8, 2021, by searching in seven electronic databases. The main outcome was all-cause mortality occurred during hospitalization. Data were combined using the general variance-based method on the effect estimate for each study. Separate meta-analyses according to type of COVID-19 patients (hospitalized or intensive care unit [ICU] patients), anticoagulants (mainly heparin), and regimens (therapeutic *or* prophylactic) were conducted. A total of 29 articles were selected, but 23 retrospective studies were eligible for quantitative meta-analyses. No clinical trial was retrieved. The majority of studies were of good quality; however, 34% did not distinguish heparin from other anticoagulants. Meta-analysis on 25,719 hospitalized COVID-19 patients showed that anticoagulant use was associated with 50% reduced in-hospital mortality risk (pooled risk ratio [RR]: 0.50, 95% confidence interval [CI]: 0.40–0.62; I^2: 87%). Both anticoagulant regimens (therapeutic and prophylactic) reduced in-hospital all-cause mortality, compared with no anticoagulation. Particularly in ICU patients, the anticoagulant therapeutic regimen was associated with a reduced in-hospital mortality risk (RR: 0.30, 95% CI: 0.15–0.60; I^2: 58%) compared with the prophylactic one. However, the former was also associated with a higher risk of bleeding (RR: 2.53, 95% CI: 1.60–4.00; I^2: 65%). Anticoagulant use, mainly heparin, reduced all-cause mortality in COVID-19 patients during hospitalization. Due to the higher risk of bleeding at therapeutic doses, the use of prophylactic dosages of anticoagulant is probably to be preferred in noncritically ill COVID-19 patients.

Keywords
- COVID-19
- coagulation
- heparin
- bleeding
- mortality

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Histopathological investigations of fatal cases of coronavirus disease 2019 (COVID-19) reported that the primary cause of death was respiratory failure with exudative diffuse alveolar damage and massive capillary congestion.[1,2] In addition, in these subjects, the frequent presence of extensive pulmonary interstitial fibrosis and pulmonary microthrombosis has been shown. These findings might explain the development of hypoxemia and respiratory failure, and support the concept of a hypercoagulable state in these critically ill patients.[1,3]

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appears to generate a prothrombotic condition as evidenced by different reports of arterial, venous, and pulmonary-related thrombosis in COVID-19 patients. Indeed, a high incidence of thrombotic events and bleeding complications has been reported in patients with COVID-19.[4–7] A common finding in these patients requiring hospitalization is increased levels of D-dimer (i.e., a fibrin degradation product) and a longer prothrombin time, which are both associated with a higher risk of death.[8]

Heparin is able to bind SARS-CoV-2 spike protein and could act as a competitive inhibitor for viral entry, thus decreasing virus infectivity.[9,10] In addition, heparin has anti-inflammatory effects, both at the vasculature and the airway levels, which could beneficially impact COVID-19-associated inflammation.[10] Thus, anticoagulant treatment could improve the prognosis of COVID-19 patients. Despite the versatile role of heparin as both an anticoagulant and an anti-inflammatory drug, and theoretical antiviral effect, no data from randomized clinical trials are available yet to prove the efficacy of this drug in COVID-19 patients.

Nevertheless, during the first months of pandemic outbreak, guidelines on thromboprophylaxis and anticoagulant therapy in COVID-19 were rapidly emerging, with different recommendations,[9–15] focusing mainly on prevention of venous thromboembolism (VTE) events in COVID-19 patients.

The World Health Organization, the U.S. Centers for Disease Control and Prevention, and Department of Defense recommended a prophylactic dose of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for prevention of VTE in hospitalized adults and adolescents with severe COVID-19 disease, except if contraindicated.[11–13]

The Italian Society on Thrombosis and Haemostasis[14] and a position paper endorsed by several international societies suggested VTE risk stratification for all individuals with COVID-19 and extended thromboprophylaxis postdischarge for patients at a higher risk of VTE, while recognizing insufficient evidence to recommend the empiric use of therapeutic doses of UFH and LMWH.[6,15] Others have suggested intermediate or therapeutic doses of LMWH for hospitalized patients and extended VTE prophylaxis for up to 45 days postdischarge.[15] Finally, the article by Barnes et al recommended pharmacologic VTE prophylaxis for all hospitalized nonpregnant patients with confirmed or highly suspected COVID-19, regardless of VTE risk assessment score, unless a contraindication exists; for patients who were being discharged from hospital, extended VTE prophylaxis was not suggested.[16]

Several randomized controlled clinical trials are currently ongoing,[17,18] and preliminary data have recently been published from observational studies on the use of heparins or other anticoagulant drugs with contrasting results.

We therefore conducted a systematic review and performed a meta-analysis of published studies on the effects of anticoagulant use (i.e., heparin and nonheparin anticoagulants together) on in-hospital all-cause mortality, trying also to separate *prophylactic* from *therapeutic* anticoagulant dosage, to provide clinical insights for consideration in the management of hospitalized COVID-19 patients.

Methods

This study was conducted according to the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[19] The protocol was registered at https://www.crd.york.ac.uk/prospero/ as CRD42020212915. Institutional review board approval was not required, as the study did not directly involve human participants.

Search strategy

A flow diagram for study selection is reported in ►**Supplementary Fig. S1**. Articles published in Medline, Embase, PubMed, Web of Science, Cochrane Central Database, MedRxiv, and Preprints.org were retrieved until January 8, 2021. Studies were restricted to humans, and their titles and/or abstracts contained at least one of the following terms: "coronavirus," "COVID-19," or "SARS-CoV-2," plus the term "heparin," "anticoagulant treatment," or "low molecular weight," or "oral anticoagulant," or "direct thrombin inhibitors," plus the term "mortality," "death," or "survival." An assessment of references was also conducted. Additionally, we searched peer-reviewed international congress abstracts in the dedicated section on COVID-19.

We identified 330 publications. To be included in this systematic review, the study had to (1) include only COVID-19 patients and (2) report qualitative and/or quantitative findings on the association of heparin (mentioned as such) or an anticoagulant treatment (including heparin or not) with mortality in COVID-19 patients.

Two of us (S.C. and R.P.) independently reviewed the identified studies, then jointly excluded the articles not adhering with one or both criteria and agreed on a final selection of 29 studies,[20–48] including three published as preprints in *MedRxiv*, the preprint server for health science,[21,24,45] and one congress abstract.[27] No randomized controlled clinical trial was retrieved.

Assessment of Methodological Quality

Two investigators (S.C. and R.P.) independently assessed the methodological quality of each study by using the Newcastle–Ottawa Scale (NOS),[49] developed to assess quality of nonrandomized studies such as cohort and case–control studies. The NOS rating for each study was then converted to the Agency for Healthcare Research and Quality standard.[50] Disagreements were resolved by consensus or by a third investigator (A.D.C.), if consensus could not be reached.

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Meta-Analysis: Data Extraction and Data Analysis

The main meta-analysis was performed considering all studies that reported adjusted estimates of the effects of anticoagulant treatment on in-hospital all-cause mortality compared with no anticoagulant use in hospitalized COVID-19 patients. When both prophylactic and therapeutic dosages were compared with a referent group formed by nontreated patients, we included in the meta-analysis the effect estimate of the prophylactic dose.[35,36,39] We performed different meta-analyses according to the characteristics of COVID-19 patients (all patients hospitalized or treated in the intensive care unit [ICU]) and to different types of anticoagulant dosage (therapeutic *or* prophylactic regimens). We also performed a subgroup meta-analysis considering only the studies that reported the association of specified heparin (i.e., LMWH and UFH) treatment with in-hospital all-cause mortality.

A secondary meta-analysis was performed considering as outcome the bleeding events, the most representative adverse effect of anticoagulant use. In this case, the numbers of events in both anticoagulant and control groups were extracted and used to calculate risk ratio (RR) and 95% confidence intervals (CIs) for each selected study.

All analyses were performed using standard statistical procedures provided in RevMan5.4 (the Cochrane Collaboration, Oxford, United Kingdom). Data were combined using the general variance-based method that requires information on the effect estimates and their 95% CI from each study. In addition, 95% CIs were used to assess the variance and the relative weight of each study. Heterogeneity was assessed using the Higgins' I^2 metric. When the heterogeneity among studies appeared to be high ($I^2 > 60\%$), results from the random effects model only were considered. The hypothesis that publication bias might have affected the validity of the estimates was visually tested by a funnel plot-based approach (►**Supplementary Fig. S2**).

Results

Characteristics of the Studies

The general characteristics of the 29 studies are shown in ►**Tables 1** and **2**.

Four studies were from China,[20,21,42,47] 14 from Europe,[22,23,28,29,31,32,34,35,40,41,43,44,46,48] and 11 from United States (►**Table 1**).[24–27,30,33,36–39,45] All were retrospective observational studies. Studies included ICU or hospitalized COVID-19 patients, except for the study by Tremblay et al that included both ambulatory and hospitalized COVID-19 patients.[25] All studies included male and female adults. The sample size ranged from 26 to 4,389 patients (►**Table 1**). In general, the studies collected retrospective data (i.e., treatment, outcome, comorbidity, COVID-19 severity) from patient electronic medical records and defined mortality as death occurred during hospitalization for any cause ("overall" or "all-cause"). In particular, the majority of the studies ($N = 25$) considered in-hospital all-cause mortality as the primary outcome (►**Table 2**), while the remaining focused mainly on thrombotic or bleeding complications[21,22,28] or on acute respiratory distress syndrome.[29]

Eighteen studies reported data exclusively for heparin (UFH or LMWH) treatment.[20–23,28,30–32,34,35,40–44,46–48] Six studies investigated the role of any anticoagulant treatment, including LMWH or UFH, direct thrombin inhibitors, and/or direct oral anticoagulants.[24,33,36–38,45] Only one study investigated three types of anticoagulant drugs separately (i.e., apixaban, enoxaparin, UFH).[39] No information was provided on the type of anticoagulant used by the remaining four studies (►**Table 2**).[25–27,29] The studies mainly used as a reference a group formed by patients not treated with any anticoagulant.[20,21,23,25–27,29,31–37,39,41,42,45,47,48] Additionally, 13 studies compared two groups of patients at different dosages of anticoagulant (therapeutic vs. prophylactic) (►**Table 2**).[22,24,28,30,33,34,37,38,40,43,44,46,48] The studies were mostly considered of good quality (23/29) (►**Supplementary Table S1**).[50] Wide heterogeneity was found regarding the outcomes investigated (domain 3), the type of anticoagulant used, and the definition of the dosage (domains 1 and 2). In particular, each study had its own definition of therapeutic or prophylactic dosage, without a standard dosage of reference.

Qualitative Review: Association with Mortality

Anticoagulant Use versus No Anticoagulant Use

Studies comparing patients who received anticoagulants or not[20,21,23,25–27,29,31–37,39,41,42,45,47,48] differed from each other in type and dosage of treatment, and showed conflicting results (►**Table 2**). The study of Tang et al was the first that investigated the association between anticoagulant treatment and 28-day mortality in 449 Chinese COVID-19 patients (22% treated with therapeutic doses of LMWH); it reported that anticoagulant therapy was associated with a better prognosis only in severe COVID-19 patients with a higher risk of sepsis-induced coagulopathy or with markedly elevated D-dimer levels.[20]

Among the studies considering all hospitalized COVID-19 patients ($N = 15$), the majority reported that anticoagulant treatment was associated with lower in-hospital all-cause mortality (►**Table 3**).[23,26,31–37,39,41,42,45,47,48] In particular, three studies conducted in large settings of hospitalized COVID-19 patients showed that anticoagulant treatment, either at therapeutic or prophylactic doses, was associated with a reduced risk of in-hospital mortality, compared with no anticoagulant treatment (►**Table 3**).[36,37,48] Billett et al, investigating the efficacy of three types of anticoagulant drugs (i.e., apixaban, enoxaparin, UFH) on in-hospital mortality in COVID-19 hospitalized patients, observed that apixaban and enoxaparin had similar beneficial effects on that outcome.[39]

On the contrary, the study of Tremblay et al concluded that anticoagulant therapy alone was unlikely to be protective for COVID-19-related morbidity and all-cause mortality.[25] However, the latter study considered both outpatients and hospitalized COVID-19 patients and had a sample size relatively

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Table 1 General characteristics of the 29 selected studies on anticoagulant treatment and risk of in-hospital mortality in COVID-19 patients

Study	Country	Time period	Type of COVID-19 patients	*N*	Sex, male %	Age (y), mean (SD)
Tang et al[20] J Thromb Haemost 2020, April 27	China	From Jan. 1 to Feb. 13, 2020	Severe COVID-19 patients	449	59.7	65.1 (12.0)
Liu et al[21] Preprint from medRxiv 2020, April 28	China	From Feb. 8 to Mar. 18, 2020	ICU patients	61	67.2	72 (10)
Llitjos et al[22] J Thromb Haemost 2020, May 27	France	From Mar. 19 to Apr. 11, 2020	ICU patients	26	77.0	Median 68 IQR: 51.5–74.5
Ayerbe et al[23] J Thromb Thrombolysis 2020, May 31	Spain	From Mar. 1 to Apr. 20, 2020	All patients	2,075	60.5	67.6 (15.5)
Trinh et al[24] Preprint from medRxiv 2020, June 3	United States	From Mar. 1 to Apr. 11, 2020	ICU patients	244	66.0	59.6 (13.2)
Tremblay et al[25] ASH 2020, July 2	United States	From Mar.1 to Apr. 1, 2020	Ambulatory and hospitalized COVID-19 patients	656	44.7	69.1 (13.87)
Paranjpe et al[26] JACC 2020, July 7	United States	From Mar. 14 to Apr. 11, 2020	All patients	2,773	NR	NR
			ICU patients	395		
Al-Samkari et al[27] Res Pract Thromb Haemost 2020, July 15	United States	From Mar. 4 to Apr. 11, 2020	ICU patients	2,809	64.5	Median 61 IQR: 53–71
Pesavento et al[28] J Thromb Haemost 2020, July 21	Italy	From Feb. 26 to Apr. 6, 2020	All patients	324	55.9	Median 71 IQR: 59–82
Russo et al[29] Pharmacological Research 2020, September	Italy	From Feb. to Apr. 2020	All patients	192	59.9	67.7 (15.2)
Ferguson et al[30] J Clin Pharmacol 2020, September	United States	From Mar. 15 to May 8, 2020	ICU patients	141	NR	NR
Schiavone et al[31] Int J Cardiol 2020, 8 September	Italy	From Feb. 23 to April 1, 2020	All patients	844	61.7	63.4 (16.1)
Desai et al[32] Int J of Cardiology 2020, 22 September	Italy	From Feb. 21 to April 14, 2020	All patients	575	66.1	64.8 (14.6)
Hsu et al[33] Thromb Res 2020, 23 September	United States	From Feb. 27 to Apr. 24, 2020	All patients	468	54.9	Median 65.1 IQR: 52–75.5
Gonzalez-Porras et al[34] Rev Med Virol 2020, 24 September	Spain	From Mar. 1 to April 7, 2020	All patients	690	58.8	Median 72.5 IQR: 64–85
Albani et al[35] EClinicalMedicine 2020, 5 October	Italy	From Feb. 20 to May 10, 2020	All patients	1,403	65.5	Median 70.5 IQR: 59.9–78.5
Ionescu et al[36] Eur J Haematol 2020, 11 October	United States	From Mar. 13 to May 5, 2020	All patients	3,480	48.5	64.5 (17.0)
Nadkarni et al[37] JACC 2020, 20 October	United States	From Mar. 1 to Apr. 30, 2020	All patients	4,389	66	Median 65 IQR: 53–77
Lynn et al[38] Thromb Res 2020, 5 November	United States	From Mar. 15 to May 31, 2020	All patients	402	53.7	>18

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Table 1 (*Continued*)

Study	Country	Time period	Type of COVID-19 patients	*N*	Sex, male %	Age (y), mean (SD)
Billett et al[39] Thromb Haemost 2020, 13 November	United States	From Mar. 1 to May 30, 2020	All patients	3,625	52.6	>18
Bolzetta et al[40] Aging Clin Exp Res 2020, 16 November	Italy	From Mar. 31 to May 1, 2020	All patients	81	38.1	81.4 (11.9)
Falcone et al[41] Open Forum Infect Dis 2020, 19 November	Italy	From Mar. 4 to April 30, 2020	All patients	315	76.2	70 IQR: 57–80
Qin et al[42] Thromb Res 2020, 23 November	China	From Jan 10 to Feb 28, 2020	All patients	749	48	60 (15)
Jonmarker et al[43] Crit Care 2020, 23 November	Sweden	From Mar. to April, 2020	ICU patients	152	82.2	61 IQR: 52–69
Canoglu and Saylan[44] Ann Saudi Med 2020, 3 December	Turkey	From Mar. 11 to April 30,2020	Severe COVID-19 patients	154	62.3	60 (20.5)
Rentsch et al[45] Preprint from medRxiv 2020 11 December	United States	From Mar. 1 to July 31,2020	All patients	4,297	93.4	68 IQR: 58–75
Martinelli et al[46] Intern Emerg Med 2021, 3 January	Italy	From Mar. 9 to April 7, 2020	All patients	278	65.1	59 IQR: 49–67
Shen et al[47] Cardiovasc Drugs Ther 2021 4 January	China	From Jan. 26 to Mar. 26, 2020	All patients	525	49.3	64 (19)
			ICU patients	89		
Di Castelnuovo et al[48] Thromb Haemost 2021, 7 January	Italy	From Feb. 19 to May 23, 2020	All patients	2,574	61.6	66.8 (15.2)
			ICU patients	327		

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

small ($N = 656$). Finally, Russo et al observed that anticoagulant treatment prior to hospital admission did not affect the risk of death during hospitalization (RR: 1.15, 95% CI: 0.29–2.57).[29]

Five studies investigated ICU COVID-19 patients.[21,26,27,47,48] A study from a single center in the United States reported that the incidence of in-hospital mortality was 29.1% for those treated with anticoagulants as compared with 62.7% in patients who did not receive anticoagulant treatment.[26] In particular, two recent studies found that in-hospital LMWH treatment was associated with a lower mortality in ICU COVID-19 patients (►**Table 2**).[47,48] In contrast, Al-Samkari et al failed to show any difference in survival rate between treated and untreated groups, in a greater cohort of 2,809 subjects.[27] Finally, the non-peer–reviewed study by Liu et al based on a small sample size of only 61 COVID-19 patients showed that LMWH treatment led to severe thrombocytopenia with fatal outcome (25/61 had severe thrombocytopenia, of whom 96% did not survive).[21]

Therapeutic versus Prophylactic Dosage

Thirteen studies compared two different dosages of anticoagulant treatment.[22,24,28,30,33,34,37,38,40,43,44,46,48] The definitions of therapeutic or prophylactic dose were different among studies (►**Table 2**). In the majority of the works reporting heparins' dosages (66%), the prophylactic dosage included UFH <5,000 IU; enoxaparin 20 to 40 mg/daily or 1 mg/kg/daily; therapeutic dosage included 5,000 > UFH < 15,000 IU; enoxaparin > 40 mg/daily or 1 mg/kg twice or three times daily (►**Table 2**).[24,30,34,37,38,44,46,48]

The study by Pesavento et al reported that the rate for overall mortality was 12.2 (95% CI: 8.1–17.8) per 100 persons/month in patients who received LMWH prophylactic doses and 20.1 (95% CI: 11.0–33.8) per 100 persons/month in those treated with higher doses, defined as subtherapeutic.[28] Di Castelnuovo et al showed that both prophylactic and therapeutic regimens were effective in reducing mortality, the prophylactic doses to a higher extent (HR: 1.54, 95% CI: 1.06–2.25).[48]

Similar results were observed by Hsu et al, showing that the group who received a therapeutic anticoagulant had a higher 30-day mortality compared with those receiving standard and high-intensity prophylaxis (40 vs. 15 vs. 6%, respectively, $p < 0.001$).[33] Finally, the study by Lynn et al reported that therapeutic anticoagulation did not provide in-hospital mortality benefit over thromboprophylaxis, independent of comorbidities or disease severity.[38]

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Table 2 Type and dosage of anticoagulant treatment and main quantitative results of the 29 selected studies

Study	Exposure	Comparison	Reported treatment description	Mortality	Main quantitative results	Adjustment
Tang et al[20]	Therapeutic LMWH	No heparin	• 94 patients had 40–60 mg enoxaparin/d • 5 patients had 10,000–15,000 U/d of UFH • All patients were treated for 7 days or longer	Primary outcome 28-day mortality	OR: 1.65 95% CI: 0.93–2.92	Age, sex, with underlying diseases, prothrombin time, platelet count, D-dimer
Liu et al[21]	LMWH	No heparin	NR	Secondary outcome Overall mortality	NR	–
Llitjos et al[22]	Therapeutic LMWH	Prophylactic LMWH	• *Therapeutic AC:* LMWH or UFH with anti-Xa monitoring, with therapeutic levels of 0.3–0.7 U/mL of anti-Xa activity • *Prophylactic AC:* NR	Secondary outcome Overall mortality	NR	–
Ayerbe et al[23]	Heparin	No heparin	• NR	Primary outcome In-hospital mortality	OR: 0.42 95% CI: 0.26–0.67	Age and gender, temperature and saturation of oxygen on admission
Trinh et al[24]	Therapeutic AC	Prophylactic AC	• *Therapeutic AC:* infusions of 15 U/kg/h or greater with or without a heparin bolus of 80 U/kg with the goal to achieve an activated prothrombin time of 70–100 seconds based on institutional protocol. Therapeutic enoxaparin dose was defined as 1 mg/kg twice daily if the GFR was >30 mL/min or once daily if the GFR ≤30 mL/min • *Prophylactic AC:* heparin 5,000 U subcutaneously two to three times daily, or enoxaparin 40 mg twice daily if the GFR >30 mL/min or 40 mg once daily if GFR ≤30 mL/min. Newly initiated apixaban 2.5 mg or 5 mg twice daily was considered prophylactic dosing	Primary outcome In-hospital mortality	HR: 0.209 95% CI: 0.10–0.46	Propensity score matched patients: anticoagulation for 5 days, age, gender, history of chronic kidney disease, changes in creatinine over time, asthma, concurrent therapies (corticosteroids, tocilizumab), lactate, baseline SOFA score, and time from intubation day
Tremblay et al[25]	Therapeutic AC	No AC	• NR	Primary outcome All-cause mortality	HR: 1.21 95% CI: 0.75–1.95	Propensity score-matched patients: age, sex, race, CCI, and obesity
Paranjpe et al[26]	AC	No AC	• NR	Primary outcome In-hospital mortality	NR	Adjusted, without description of confounders
Al-Samkari et al[27]	Therapeutic AC	No AC	• NR	Primary outcome 28-day mortality	HR: 1.12 95% CI: 0.92–1.36	Adjusted, without description of confounders.
Pesavento et al[28]	Prophylactic LMWH	Subtherapeutic LMWH	• *Prophylactic LMWH:* daily doses of UFH up to 15,000 U, of enoxaparin up	Secondary outcome All-cause mortality	Incident rate	NR

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Table 2 (*Continued*)

Study	Exposure	Comparison	Reported treatment description	Mortality	Main quantitative results	Adjustment
			to 4,000 U, and of fondaparinux up to 2.5 mg. • *Subtherapeutic LMWH:* higher daily doses, usually adjusted to body weight or laboratory parameters, regardless of the drug amount.			
Russo et al[29]	AC	No AC	• Preadmission therapy	Secondary outcome In-hospital mortality	RR: 1.15 95% CI: 0.29–2.57	Propensity score-matched patients: age, smoke, and comorbidities
Ferguson et al[30]	Therapeutic LMWH	Prophylactic LMWH	• *Therapeutic anticoagulation:* as either a continuous infusion of heparin dose-adjusted based on UFH levels, or by subcutaneous 1 mg/kg twice daily or 1.5 mg/kg daily LMWH • *Prophylactic anticoagulation:* enoxaparin 40 mg subcutaneously daily, enoxaparin 30 mg twice daily, enoxaparin 0.5 mg/kg twice daily, or heparin 5,000 U subcutaneously two or three times daily.	Primary outcome 28-day mortality	ICU pz: HR: 0.73; 95% CI: 0.33–1.76	Adjusted, without description of confounders
Schiavone et al[31]	Heparin	No heparin	• NR	Primary outcome In-hospital mortality	OR: 0.60; 95% CI: 0.38–0.94	NR
Desai et al[32]	Heparin	No heparin	• NR	Primary outcome In-hospital mortality	HR: 0.51 95% CI: 0.34–0.76	Age, gender, comorbidities, time interval between onset of symptoms and admission and treatments provided.
Hsu et al[33]	No AC	Prophylactic AC	• *Therapeutic anticoagulation:* intravenous heparin, LMWH 1 mg/kg twice daily, dose-adjusted warfarin with a target INR of 2.0–3.0, apixaban 5 mg twice daily, or rivaroxaban 20 mg daily. • *Prophylactic anticoagulation:* LMWH 40 mg once daily, UFH subcutaneous 5,000 U three times daily, or apixaban 2.5 mg twice daily.	Primary outcome 30-day mortality	RR: 2.09 95% CI: 0.77–5.67	Adjusted, without description of confounders
	Therapeutic AC	Prophylactic AC			RR: 1.05 95% CI: 0.55–2.02	
Gonzalez-Porras et al[34]	No LMWH	Therapeutic LMWH	• *Therapeutic anticoagulation:* 1 mg/kg enoxaparin/daily or bemiparin 5,000 U/daily. Patients with creatinine clearance (CLCr) <30 mL/min: enoxaparin or bemiparin was administered at 0.5 mg/kg or 3,500 U subcutaneously once daily, respectively. • *Prophylactic anticoagulation:*	Primary outcome In-hospital mortality	OR: 6.24 95% CI: 2.65- 14.68	Adjusted, without description of confounders
	Prophylactic LMWH	Therapeutic LMWH			OR: 2.07 95% CI: 1.17- 3.68	

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Table 2 (*Continued*)

Study	Exposure	Comparison	Reported treatment description	Mortality	Main quantitative results	Adjustment
			enoxaparin 40 mg or bemiparin 3,500 U subcutaneously once daily; if they had a CLCr <30 mL/min upon initiation of LMWH, patients received enoxaparin 20 mg or bemiparin 2,500 units SC once daily			
Albani et al[35]	Therapeutic LMWH	No heparin	• *Therapeutic anticoagulation:* more than 40 mg of enoxaparin per day • *Prophylactic anticoagulation:* 40 mg of enoxaparin per day	Primary outcome In-hospital mortality	OR: 0.54 95% CI: 0.38–0.76	Propensity score-matched for age, sex, PaO2/FiO2, lactate, C-reactive protein, platelets, ICU admission, and treatment with corticosteroids, azithromycin, or hydroxychloroquine
	Prophylactic LMWH	No heparin			OR: 0.50 95% CI: 0.36–0.69	
Ionescu et al[36]	Therapeutic AC	No AC	• *Therapeutic anticoagulation:* intravenous UFH with at least one documented activated partial thromboplastin time in the anticoagulation range (≥45 seconds); subcutaneous enoxaparin at doses of 1 mg/kg twice daily or 1.5 mg/kg once daily; intravenous argatroban infusion; subcutaneous fondaparinux at doses of 5–10 mg once daily (weight-based dosing); oral anticoagulants prescribed prior to and continued throughout hospitalization • *Prophylactic anticoagulation:* subcutaneous injection of UFH at doses of 5,000 U twice or three times daily; subcutaneous enoxaparin injection at doses of 30–40 mg once daily; subcutaneous fondaparinux at a dose of 2.5 mg once daily.	Primary outcome In-hospital mortality	HR: 0.14 95% CI: 0.05–0.23	Propensity score adjusted for age (years), sex, race, body mass index, and comorbid conditions
	Prophylactic AC	No AC			HR: 0.35 95% CI: 0.22–0.54	
Nadkarni et al[37]	AC	No AC	• *Therapeutic anticoagulation:* continuous intravenous infusions of bivalirudin, argatroban, or UFH, high-dose LMWH (specifically enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily), apixaban 5 mg twice daily, rivaroxaban or dabigatran. For patients >75 years, apixaban was considered therapeutic at lower doses: at 2.5 mg twice a day or 5 mg once a day. • *Prophylactic anticoagulation:* subcutaneous UFH, LMWH once daily, or apixaban (2.5 mg twice a day or 5 mg daily in patients ≤75 years).	Primary outcome In-hospital mortality	HR: 0.50 95% CI: 0.45–0.57	Adjusted hazard ratio without description of cofounders. IPTW models
	Therapeutic AC	Prophylactic AC			HR: 0.86 95% CI: 0.73–1.02	

(*Continued*)

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Table 2 (*Continued*)

Study	Exposure	Comparison	Reported treatment description	Mortality	Main quantitative results	Adjustment
Lynn et al[38]	Therapeutic AC	Prophylactic AC	• *Therapeutic anticoagulation:* 1 mg/kg twice a day or 1.5 mg/kg daily subcutaneous enoxaparin, and direct oral anticoagulants • *Prophylactic anticoagulation*: NR	Primary outcome In-hospital mortality	Unadjusted OR: 3.42 95% CI: 2.06–5.67	NR
Billett et al[39]	Therapeutic LMWH	No heparin	• *Therapeutic LMWH:* enoxaparin ≥1 mg/kg b.i.d. or ≥1·5mg/kg daily when GFR≥30, or ≥ 0·7mg/kg b.i.d. or ≥1mg/kg daily when GFR < 30 • *Prophylactic LMWH:* enoxaparin ≤ 0.5mg/kg b.i.d. or ≤1.0mg/kg daily when GRF > ≥30, or ≤ 0.35mg/kg b.i.d. or≤ 0.7mg/kg daily when GFR < 30	Primary outcome In-hospital mortality	OR: 0.83 95% CI: 0.44–1.56	Multivariate logistic regression adjusted for age, oxygen saturation, eGFR, D-dimer, time period, and ventilator requirement
	Prophylactic LMWH	No heparin			OR: 0.49 95% CI: 0.32–0.73	
Bolzetta et al[40]	Therapeutic LMWH	Prophylactic LMWH	Heparins: calciparin, fondaparinux, and enoxaparin	Primary outcome In-hospital mortality	HR: 0.89 95% CI: 0.30–2.71	Cox regression model adjusted for age, sex, obesity, diabetes, and comorbid conditions
Falcone et al[41]	LMWH	No heparin	• *Therapeutic LMWH:* enoxaparin 40–60 mg twice daily • *Prophylactic LMWH:* enoxaparin 40–60 mg daily	Primary outcome 30-day mortality	HR: 0.27 95% CI: 0.12–0.62	Propensity score adjusted for age, male sex, CCI, lymphocytes, platelets count, troponin value during the first 48 hours, PiO2/FiO2 ratio on admission and all treatments
Qin et al[42]	LMWH	No heparin	• *Therapeutic LMWH*: 100 U/kg, q12h • *Prophylactic LMWH:* 3,000–5,000 U/d	Primary outcome 28-day mortality	HR: 0.22 95% CI: 0.09–0.55	Cox regression model. Adjusted hazard ratio without description of cofounders
Jonmarker et al[43]	Therapeutic LMWH	Prophylactic LMWH	• *Therapeutic LMWH*: tinzaparin >175 IU/kg or dalteparin >200 IU/kg • *Prophylactic LMWH:* tinzaparin 2,500–4,500 IU or dalteparin 2,500–5,000 IU	Primary outcome 28-day mortality	HR: 0.33 95% CI: 0.11–1.00	Cox regression model adjusted for sex, age, body mass index, SAPS III, invasive respiratory support, and initial dosing of thromboprophylaxis
Canoglu and Saylan[44]	Prophylactic LMWH	Therapeutic LMWH	• *Therapeutic LMWH*: enoxaparin 1 mg/kg twice daily • *Prophylactic LMWH:* enoxaparin 0.5 mg/kg twice daily	Primary outcome In-hospital mortality	OR: 6.5 95% CI: 2.4–17.6	Multiple logistic regression adjusted for age, comorbidities, LMWH prophylactic dose, D-dimer, aPTT, and platelets
Rentsch et al[45]	AC	No AC	• 1,094 patients treated with heparin SC: 5,000 units b.i.d. or t.i.d. • 2,506 patients: enoxaparin 40 mg q.d. or 30 mg b.i.d. • 4 patients: fondaparinux 2.5 mg q.d. • 21 patients: apixaban 2.5 mg b.i.d. • 2 patients: rivaroxaban 10 mg q.d. or 2.5 mg b.i.d. for arterial disease	Primary outcome In-patient mortality	HR: 0.69 95% CI: 0.61–0.77	IPTW Cox regression model adjusted for information on age, race/ethnicity, sex, urban/rural residence, comorbidities, CCI, and substance use.

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Table 2 (*Continued*)

Study	Exposure	Comparison	Reported treatment description	Mortality	Main quantitative results	Adjustment
Martinelli et al[46]	Therapeutic LMWH	Prophylactic LMWH	• *Therapeutic LMWH*: enoxaparin for those in ICU 1 mg/kg twice daily, those in high-intensity of care wards 0.7 mg/kg twice daily and those in low-intensity of care wards 1 mg/kg daily • *Prophylactic LMWH:* enoxaparin 40 mg daily increased to 60 mg daily in obese	Primary outcome In-hospital mortality	HR: 0.36 95% CI: 0.18–0.76	Adjusted hazard ratio without description of cofounders
Shen et al[47]	LMWH	No heparin	• LMWH: enoxaparin 40 mg SC once and/or twice daily	Primary outcome In-hospital mortality	OR: 0.18 95% CI: 0.10–0.30 ICU pz OR: 0.32 95% CI: 0.15–0. 0.65	Propensity score IPTW model adjusted for age, comorbidities and severity classification.
Di Castelnuovo et al[48]	LMWH	No heparin	• *Therapeutic LMWH*: fondaparinux >2.5 mg/d or enoxaparin >4,000 IU/d; higher daily doses usually adjusted to body weight or laboratory parameters *Prophylactic LMWH:* fondaparinux ≤2.5 mg/d or enoxaparin ≤4,000 IU/d	Primary outcome In-hospital 35-day mortality	HR: 0.60 95% CI: 0.49–0.74 ICU pz HR: 0.29 95% CI: 0.17–0.49	Cox proportional-hazards regression models with adjusted for age, sex, diabetes, hypertension, ischemic heart disease, chronic pulmonary disease, chronic kidney disease, C-reactive protein, HCQ, and other in-hospital therapies for COVID-19
	Therapeutic LMWH	No heparin			HR: 0.57 95% CI: 0.38–0.86	
	Prophylactic LMWH	No heparin			HR: 0.40 95% CI: 0.30–0.52	
	Therapeutic LMWH	Prophylactic LMWH			HR: 1.54 95% CI: 1.06–2.25	

Abbreviations: AC, anticoagulant; b.i.d, twice a day; CCI, Charlson Comorbidity Index; CI, confidence interval; ClCr, creatinine clearance; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; HR, hazard ratio; ICU, intensive care unit; IPTW, inverse probability treatment weighted; LMWH, low-molecular-weight heparin; NR, not reported; OR, odds ratio; PA, prophylactic anticoagulant; PZ, patients; RR, risk ratio; SAPS III, Simplified Acute Physiology Score III; SC, subcutaneous; SOFA, sequential organ failure assessment; TA, therapeutic anticoagulant; t.i.d, three times a day; UFH, unfractionated heparin.

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Table 3 Main conclusions and limitations of the 29 selected studies

Study	Main conclusions	Limitations	Newcastle–Ottawa Score system
Tang et al[20]	+ No difference in the 28-day mortality was found between heparin users and nonusers (30.3 vs. 29.7%). AC therapy mainly with LMWH appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer.	Concomitant therapies of anti-COVID-19 were not evaluated. The cohort included only severe COVID-19 patients.	9
Liu et al[21]	– Exposure to a high dose of heparin may trigger further severe thrombocytopenia with a fatal outcome. An alternative anticoagulant other than heparin should be used to treat COVID-19 patients in critical condition.	Not peer reviewed. Small sample size. Dosage of treatment is not reported. Mortality was not primary outcome.	3
Llitjos et al[22]	– High rate of thromboembolic events in COVID-19 patients treated with therapeutic anticoagulation. Our results support to consider routine screening of VTE in severe ICU COVID-19 patients.	Small sample size. Definitions of therapeutic and prophylactic heparin doses are not reported. Mortality was not primary outcome.	3
Ayerbe et al[23]	++ The administration of heparin was associated with lower mortality in patients admitted with COVID-19	Type and dosage of treatment not reported. Assessment of the outcome not specified.	9
Trinh et al[24]	++ Therapeutic anticoagulation is associated with a survival advantage among patients with COVID-19 who require mechanical ventilation in ICU. There was a trend toward increased risk of bleeding in the TA group.	Not peer reviewed. Assessment of the outcome not specified.	8
Tremblay et al[25]	– Our results suggest that AC alone is unlikely to be protective for COVID-19-related morbidity and mortality.	The cohort included both ambulatory and hospitalized patients. Type and dosage of AC not reported.	8
Paranjpe et al[26]	++ Our findings suggest that systemic AC may be associated with improved outcomes (including mortality) among patients hospitalized with COVID-19.	Type and dosage of AC not reported.	5
Al-Samkari et al[27]	-/+ Receipt of therapeutic anticoagulation early after ICU admission did not affect survival.	Definitions of therapeutic and prophylactic dosages of heparin are not reported. Type of heparin not reported.	6
Pesavento et al[28]	– The subtherapeutic dose had a higher incidence rate of mortality than the prophylactic one. – In addition, the higher doses of anticoagulants simultaneously increased the bleeding events in both MB and CRNMB.	Mortality was not primary outcome. Risk analysis was not performed. There is not a control group without exposure.	7

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Table 3 (*Continued*)

Study	Main conclusions	Limitations	Newcastle–Ottawa Score system
Russo et al[29]	-/+ Preadmission anticoagulant treatment did not affect the risk of death during hospitalization in patients with COVID-19.	Anticoagulant treatment is considered in preadmission context. Type and dosage of treatment are not reported. Mortality was not primary outcome.	5
Ferguson et al[30]	+/− Therapeutic anticoagulant did not improve the 28-day mortality when compared with the prophylactic dose. – Patients who received therapeutic anticoagulation experienced five episodes of clinically apparent bleeding. Those who received prophylactic dose anticoagulation experienced four episodes of clinically apparent bleeding.	Adjustments of analyses not reported. Concomitant therapies were not evaluated.	8
Schiavone et al[31]	+ The use of heparin was associated with a better chance of survival to hospital discharge in COVID-19 patients.	Type and dosage of treatment are not reported. Adjustments of analyses not reported.	6
Desai et al[32]	++ Treatment with LMWH was found to be protective in COVID-19-hospitalized patients.	Dosage of anticoagulant is not reported Small sample size.	9
Hsu et al[33]	– The 30-day mortality was significantly lower among all patients who received high-intensity thromboprophylaxis vs. those who received standard prophylaxis. +/− Patients who initially received high-intensity prophylaxis or therapeutic anticoagulation had improved 30-day mortality without increased rates of bleeding.	Adjustments of analyses not reported. Small sample size.	9
Gonzalez-Porras et al[34]	++ The administration of LMWH at the time of admission significantly reduced the mortality rate in unselected adult COVID-19 patients. Moreover, the magnitude of the benefit was greater for the group of patients who received high-dose heparin. – Of note, the overall major bleeding rate was more frequently reported in the high-dose group, but only one fatal event was reported.	Not peer reviewed. Adjustments of analyses not reported.	9
Albani et al[35]	++ Treatment with enoxaparin is associated with a reduced mortality in patients admitted to our hospital with diagnosis of COVID-19, compared with no enoxaparin treatment.	–	9

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Table 3 (*Continued*)

Study	Main conclusions	Limitations	Newcastle–Ottawa Score system
Ionescu et al[36]	++ Both prophylactic and therapeutic ACs were associated with decreased mortality in COVID-19. Patients receiving therapeutic doses had higher survival probability compared with those receiving prophylactic doses, and the greatest effect was observed in critically ill patients. – Major bleeding events occurred more frequently in patients receiving TA.	Precise indication for the initiation of therapeutic AC was not available. Patients treated with therapeutic dose less than 3 days were included in the prophylactic group TA in the PA group.	8
Nadkarni et al[37]	++ Both therapeutic and prophylactic anticoagulant groups had a reduced in-hospital mortality compared with no anticoagulation. Therapeutic AC was associated with a nonsignificant 14% reduction in hazard of mortality compared with prophylactic AC. – The proportion of patients with bleeding events after initiation of AC treatment was highest in patients on therapeutic AC as compared with patients on prophylactic AC and no AC.	Discrepancies between regimens of treatment wherein doses may not have accurately represented therapeutic and prophylactic AC. Patients who were on both therapeutic and prophylactic doses of AC were excluded due to inability to definitively categorize them.	9
Lynn et al[38]	– Increased mortality was associated with therapeutic AC compared with prophylactic AC. Approximately 9% of patients receiving therapeutic AC experienced clinically significant bleeding or thrombocytopenia, vs. 3% in those receiving prophylactic AC.	Dosage of treatment is not fully reported. Adjusted analyses not reported. Small sample size.	5
Billett et al[39]	++ COVID-19 patients with moderate or severe illness benefit from anticoagulation showing a decreased mortality. There was no increase in transfusion requirement with any of the anticoagulants used.	The bleeding outcome was considered as transfusion requirement and this does not take into account the intracranial or critical-site bleeds that would not necessarily entail transfusion support. Assessment of the outcome not specified.	9
Bolzetta et al[40]	+/− Therapeutic doses were not associated to a better survival rate. In older people affected by COVID-19 there is no justification for using therapeutic doses instead of prophylactic ones, having a similar impact on mortality risk	Dosage of treatment is not reported. Small sample size. Assessment of the outcome not specified.	9
Falcone et al[41]	++ LMWH was associated with a reduced risk of 30-day mortality. – All patients who developed a major bleeding received therapeutic dosages of LMWH.	Small sample size. Among patients in the not treated group, 5 of them were treated with NOAC. Patients at different dosages of LMWH were considered together in the analysis.	9

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Table 3 (*Continued*)

Study	Main conclusions	Limitations	Newcastle–Ottawa Score system
Qin et al[42]	++ LMWH emerged as an independent factor for decreased 28-day mortality.	Adjustments of analyses not reported. Small sample size. Among patients starting LMWH for prophylaxis, 19 switched to therapeutic during the treatment period	7
Jonmarker et al[43]	++ Among critically ill COVID-19 patients, high-dose thromboprophylaxis was associated with a lower risk of death.	Small sample size. Patients with chronic AC at admission, for reasons different from DVT or PE, were included in the study	9
Canoglu and Saylan[44]	++ Mortality was higher in the prophylactic group compared with the therapeutic one.	Small sample size. No information on bleeding complications Different doses of LMWH used in different clinics of the same hospital.	9
Rentsch et al[45]	++ Early initiation of prophylactic anticoagulation among patients hospitalized with COVID-19 was associated with a decreased risk of mortality.	Not peer reviewed. The 93% of cohort is represented by men.	9
Martinelli et al[46]	++ The cumulative incidence rate of death was lower in patients treated with high enoxaparin doses than in those with the standard dose. – Four patients of the high enoxaparin dose had major bleeding events. No bleeding event was observed in the standard dosage prophylaxis group.	Small sample size. Different types of therapeutic dosage according to different types of patients (ICU, high-intensity and low-intensity care ward).	9
Shen et al[47]	++ Among hospitalized COVID-19 patients, LMWH use was associated with lower all-cause in-hospital mortality than non-LMWH users. The survival benefit was particularly significant among more severely ill patients.	Small sample size. Two different dosages considered together.	9
Di Castelnuovo et al[48]	++ The heparin use was associated with lower mortality in hospitalized COVID-19 patients	Timing of the first dose of heparin at admission and duration of treatment could not be provided by some clinical centers. Specific reasons why patients were treated or not with heparin could not be collected	9

Abbreviations: AC, anticoagulant; CRNMB, clinical relevant non major bleeding; DVT, deep vein thrombosis; ICU, intensive care unit; LMWH, low-molecular-weight heparin; MB, major bleeding; NOAC, non-vitamin K oral anticoagulant; PA, prophylactic anticoagulant; SIC, sepsis-induced coagulopathy; TA, therapeutic anticoagulant; VTE, venous thromboembolism.

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On the contrary, Gonzalez-Porras et al and Martinelli et al demonstrated that the benefit of the administration of LMWH on in-hospital mortality was higher for the groups receiving the higher doses.[34,46] The study by Nadkarni et al reported a not statistically significant reduction of in-hospital mortality risk, when therapeutic anticoagulant treatment was associated with the prophylactic regimen (HR: 0.86, 95% CI: 0.73–1.02; ►**Table 2**).[37] Finally, Bolzetta et al indicated that in a cohort of elderly affected by COVID-19, there was no justification for using therapeutic instead of prophylactic doses, having a similar impact on in-hospital mortality risk (HR: 0.89, 95% CI: 0.30–2.71) (►**Table 2**).[40]

The five studies that included only ICU patients showed opposite findings,[22,24,30,43,44] and two of them were of low quality (►**Supplementary Table S1**). The small study of Llitjos et al did not consider overall mortality as a primary outcome; however, it reported the same incident rate in both heparin dosage treatment groups, but the therapeutic dose of heparin (LMWH or UFH) resulted in a higher rate of thromboembolic events in COVID-19 patients.[22] On the contrary, Trinh et al (a non-peer–reviewed study), Jonmarker et al, and Canoglu and Saylan observed that therapeutic anticoagulation was associated with survival advantage among ICU patients with COVID-19.[24,43,44] Finally, the study by Ferguson et al reported that therapeutic anticoagulation did not improve mortality at 28 days compared with the prophylactic dosage (HR: 0.73, 95% CI: 0.33–1.76).[30]

Qualitative Review: Anticoagulant Use and Bleeding in COVID-19 Patients

Several studies reported incidence of different types of bleeding (gastrointestinal, intracranial, mucocutaneous, and bronchopulmonary) which occurred during the hospitalization period of COVID-19 patients treated with anticoagulants.[24,28,30,33,34,36–38,41–43,46,47] The majority of the articles reported that treatment with a therapeutic/higher dosage of anticoagulants was associated with a higher incidence of bleeding.[28,30,34,36–38,41,46] Qin et al observed that occurrence of bleeding events was higher in the group treated with LMWH compared with the nontreated.[42] In addition, the study by Trinh et al showed that there was a trend toward increased risk of bleeding in the therapeutic group.[24] On the other hand, the study by Hsu et al showed that there was no difference in the incidence of bleeding events between therapeutic and prophylactic groups.[33] In addition, Jonmarker et al reported that bleeding events occurred more frequently in the low LMWH dose group (11.9%) than in the high-dose group (2.7%), although the findings were not statistically significant ($p = 0.16$).[43]

Quantitative Meta-Analysis

Of the 29 selected studies mentioned above, 16 were included in the main, quantitative meta-analysis (anticoagulant use vs. no anticoagulant use).[20,23,27,31–37,39,41,42,45,47,48] A secondary analysis based on 10 studies[24,30,33,34,37,40,43,44,46,48] was performed to compare different dosages of anticoagulants (therapeutic vs. prophylactic). In addition, we separately investigated the association of prophylactic and therapeutic anticoagulant regimens with in-hospital mortality, compared with the nontreated control group.

The studies by Liu et al, Llitjos et al, Pesavento et al, and Lynn et al were excluded because the adjusted associations of anticoagulant use with in-hospital all-cause mortality were not reported.[21,22,28,38] The study by Paranjpe et al[26] was excluded as part of another study already included.[37] Since the study by Tremblay et al[25] included both outpatients and hospitalized patients and the report by Russo et al[29] considered anticoagulant treatment only in the preadmission context, they were both excluded from our meta-analyses.

►**Fig. 1** shows that by pooling all the 16 selected studies, the use of anticoagulant was associated with a reduced in-hospital all-cause mortality risk of 50% (pooled RR: 0.50, 95% CI: 0.40–0.62; high level of heterogeneity: I^2: 87%, random effects model). Results from fixed effects analysis are reported in ►**Supplementary Fig. S3** (pooled RR: 0.60, 95% CI: 0.56–0.64; $I^{2:}$ 87%).

By pooling the 14 studies on all hospitalized COVID-19 patients, which accounted for 86.1% of the total weight (►**Fig. 1**), a 55% lower in-hospital all-cause mortality risk was found (pooled RR: 0.45, 95% CI: 0.37–0.54; high level of heterogeneity: I^2: 76%, random effects model); on the contrary, the subgroup meta-analysis considering ICU or severe patients showed no association between anticoagulant treatment and in-hospital all-cause mortality (13.9% of the weight; pooled RR: 1.23, 95% CI: 0.89–1.71; medium level of heterogeneity: I^2: 36%, random effects model). The latter finding was confirmed by including data on ICU patients from Shen et al and Di Castelnuovo et al's studies (pooled RR: 0.66, 95% CI: 0.30–1.45; I^2: 91%, random effect; ►**Supplementary Table S2** and ►**Supplementary Fig. S4**).[47,48]

In the "Meta-Analysis: Data Extraction and Data Analysis" section, we described that three of the selected studies separately reported the association with in-hospital mortality for both anticoagulant regimens and data on prophylactic dosage were extracted and considered for the main meta-analysis. Nevertheless, findings did not change when data on therapeutic regimen of these three studies were considered (pooled RR: 0.49, 95% CI: 0.39–0.62; high level of heterogeneity: I^2: 90%, random effects model; ►**Supplementary Fig. S5**). Additionally, in a further sensitivity analysis, the inclusion of nonadjusted estimate from one study originally excluded[21] did not modify the result (►**Supplementary Table S2** and ►**Supplementary Fig. S6**).

In comparison with no anticoagulant use, both treatments at prophylactic and therapeutic doses were found associated with a 58% (pooled RR: 0.42, 95% CI: 0.37–0.47; I^2: 0%; ►**Supplementary Table S2** and ►**Supplementary Fig. S7**) and 43% (pooled RR: 0.57, 95% CI: 0.38–0.86; I^2: 93%; ►**Supplementary Table S2** and ►**Supplementary Fig. S8**) lower in-hospital all-cause mortality risk, respectively.

The subgroup analysis, including 11 studies reporting exclusively heparin (LMWH or UFH) treatment ($N = 11{,}586$), confirmed that the treated group had a reduced in-hospital all-cause mortality risk compared with the

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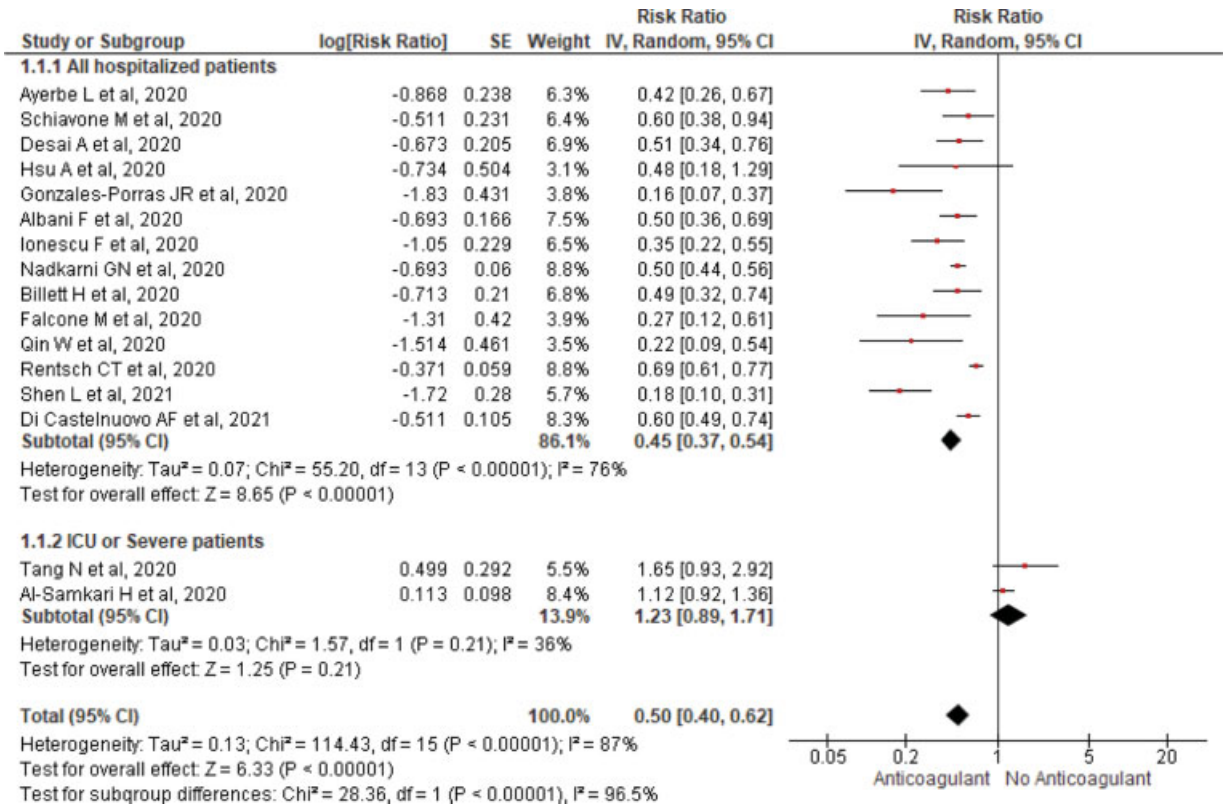

Fig. 1 Forest plot for association of anticoagulant use with in-hospital all-cause mortality in hospitalized COVID-19 patients ($N = 25{,}719$); random model.

control (pooled RR: 0.44, 95% CI: 0.33–0.59; high level of heterogeneity: I^2: 79%, random effects model; ►**Fig. 2** and ►**Supplementary Table S2**).

By pooling 10 studies on all hospitalized COVID-19 patients, a reduction of 43% in in-hospital all-cause mortality risk was found, when the therapeutic dosage was compared with the prophylactic dosage (pooled RR: 0.57, 95% CI: 0.38–0.86; high level of heterogeneity: I^2: 81%, random effect). The previous finding resulted stronger in the subgroup analysis considering four studies on ICU or severe

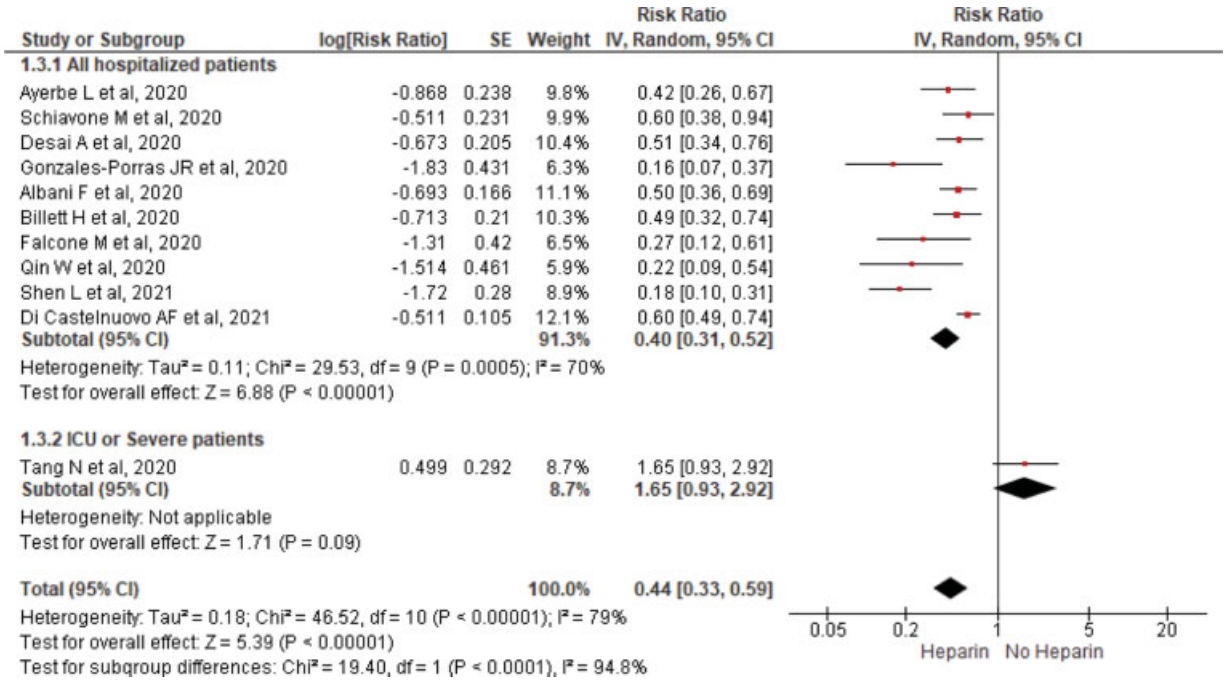

Fig. 2 Forest plot for association of heparin use with in-hospital all-cause mortality in hospitalized COVID-19 patients ($N = 11{,}586$); random model.

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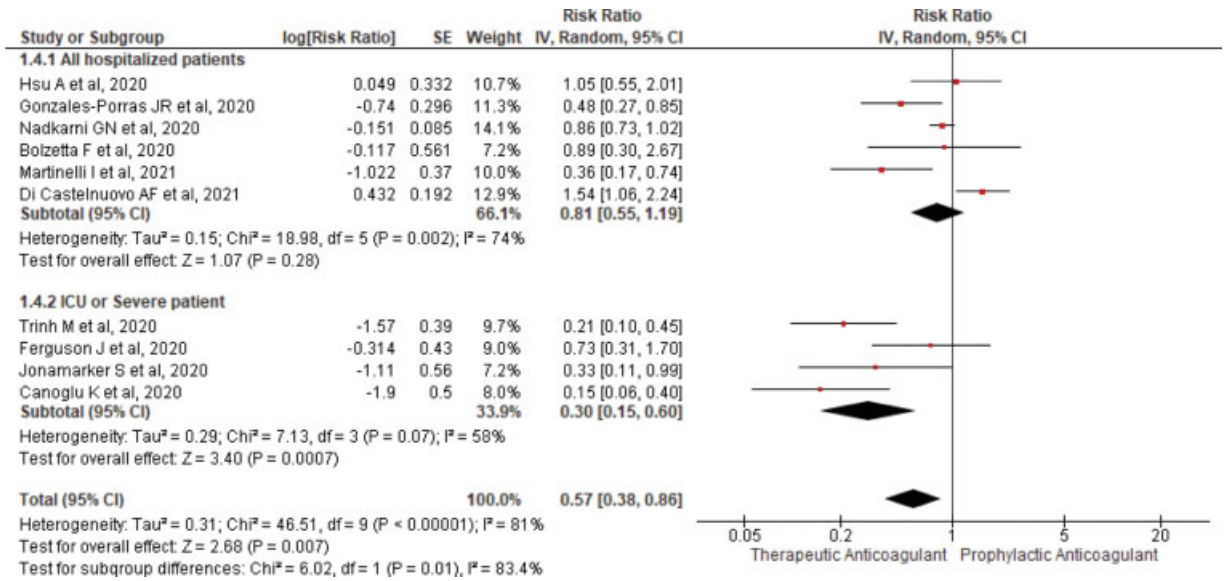

Fig. 3 Forest plot for association of two different dosages of anticoagulant (therapeutic vs. prophylactic) with in-hospital all-cause mortality in all hospitalized COVID-19 patients ($N = 6{,}113$); random model.

COVID-19 patients (pooled RR: 0.30, 95% CI: 0.15–0.60; medium level of heterogeneity: I^2: 58%) (►**Fig. 3**). Further inclusion of not adjusted studies did not change the latter finding (►**Supplementary Fig. S9**).

►**Fig. 4** shows that the anticoagulant prophylactic dosage was not associated with bleeding in comparison with no use (pooled RR: 0.77, 95% CI: 0.38–1.55; I^2: 60%, random effects model; **panel A**). On the contrary, the use of therapeutic doses of anticoagulant increased the risk of bleeding (pooled RR: 1.57, 95% CI: 1.14–2.16; I^2: 0%, random effects model; ►**Fig. 4, panel B**), compared with nontreated COVID-19 patients. A further meta-analysis confirms that

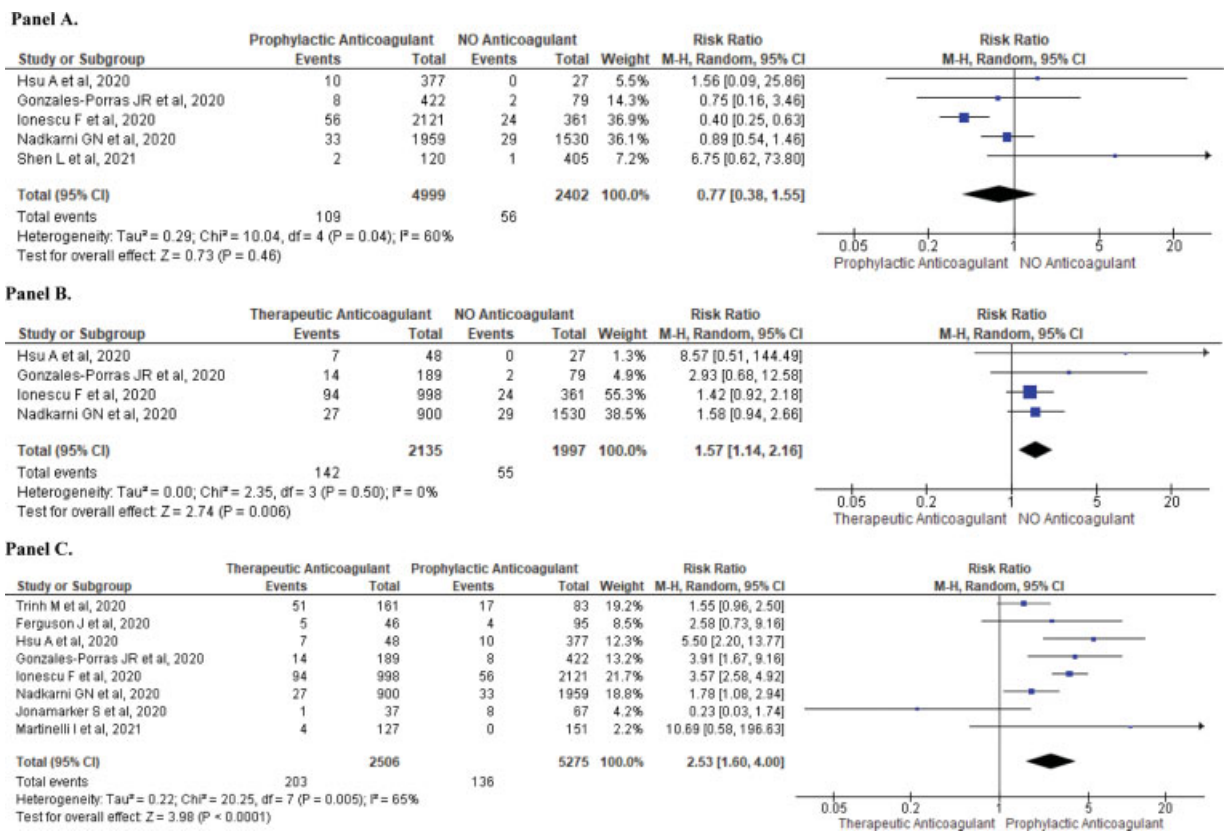

Fig. 4 **Panel A:** forest plot for association of prophylactic dosage of anticoagulants with bleeding occurrence in COVID-19 patients ($N = 7{,}401$), random model. **Panel B:** forest plot for association of therapeutic dosage of anticoagulants with bleeding occurrence in COVID-19 patients ($N = 4{,}132$), random model. **Panel C:** forest plot for association of two different dosages of anticoagulant (therapeutic vs. prophylactic) with bleeding occurrence in all hospitalized COVID-19 patients ($N = 7{,}781$); random model.

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patients treated with therapeutic doses of anticoagulants were at a higher risk of bleeding (pooled RR: 2.53, 95% CI: 1.60–4.00; I^2: 65%, random effects model; ►**Fig. 4, panel C**) compared with those at prophylactic dosages. Results from fixed effects analyses are reported in ►**Supplementary Fig. S10, panels A–C**.

Discussion

The main finding from the present analyses is that anticoagulant use, mainly as heparin, was associated with a significantly lower risk of in-hospital all-cause mortality among hospitalized COVID-19 patients.

A still open question on the use of anticoagulation in COVID-19 patients is if *therapeutic* doses of anticoagulant are more effective than the low doses used as *prophylactic*. According to our findings, both anticoagulant regimens reduced in-hospital all-cause mortality in COVID-19 patients, although the therapeutic dosage did it to a greater degree than the prophylactic, particularly when ICU patients were considered. At the same time, the therapeutic dosages were found to be associated with a higher risk of bleeding. It is well known that exposure to high doses of anticoagulant could lead to the occurrence of bleeding events, often resulting in fatal outcome.[12,14,15]

The results of our meta-analyses are in line with the recommendations of major guidelines suggesting that all hospitalized COVID-19 patients, even those not in the ICU, should receive prophylactic doses of LMWH, in the absence of contraindications.[11–13]

Recently, three meta-analyses investigated the effect of anticoagulation on in-hospital all-cause mortality in patients with COVID-19.[51–53] The first two found that anticoagulant therapy (any dosage) was not associated with increased risk of mortality. Both meta-analyses included studies that did not meet our inclusion criteria.[25,29,54–57] In particular, the meta-analysis by Lu et al, among the five selected studies ($N = 8{,}533$), included two studies reporting the effect of anticoagulant treatment in a preadmission context. However, the exclusion of these two studies[25,29] did not change the results (RR: 0.79, 95% CI: 0.48–1.31).[51] On the other hand, Salah et al used nonadjusted estimates in their meta-analysis (six studies, $N = 6{,}390$).[52]

Finally, our results are in line with recent findings by Kamel et al that showed a favorable effect of in-hospital anticoagulant treatment on in-hospital mortality in COVID-19 patients (RR:0.56, 95% CI: 0.36–0.92, five studies, $N = 4{,}229$). Additionally, they reported that the prophylactic dose might be associated with higher in-hospital mortality than the therapeutic anticoagulant (RR: 1.58, 95% CI: 1.34–1.87, three studies, $N = 963$).[53] We performed sensitivity analyses according to type of COVID-19 patients (hospitalized or ICU patients) and on exclusive heparin treatment.

Conflicting results, due to the wide heterogeneity of the study setting, population, and therapeutic approaches, underline the urgent need for randomized controlled clinical trials to define the effect of anticoagulant dosages in patients with COVID-19. In addition, the major guidelines have not yet recommended a standardized protocol for the management of COVID-19 patients. The only exception is the position paper by the Italian Society on Thrombosis and Haemostasis that defined the prophylactic dose of LMWH as enoxaparin 4,000 IU subcutaneously every 12 hours.[14] As a consequence, the only suggestions available for the choice of treatment in COVID-19 patients are based on the VTE risk stratification, the monitoring of specific laboratory parameters, (hemostasis function and platelet count), and the evaluation of the personal clinical history of each single patient.[14,16]

Strengths and Limitations

The present article has the strength of including all relevant studies not included in previous reviews until now,[27,36,37,39–48] analyzing a greater number of studies and of COVID-19 patients than those of previous studies.[51–53]

Its major limitation is that all primary studies are observational, and that subgroup analyses suffer from a high degree of heterogeneity. In particular, prophylactic and therapeutic dosages were not defined in a standardized way, as well as the assessment of major or nonmajor clinically relevant bleeding complications. Our results should therefore be considered with caution, since the possibility of confounding could not be fully excluded.

Conclusions

We report a significant reduction of in-hospital all-cause mortality in COVID-19 patients treated with anticoagulants (mainly heparin). Both anticoagulant regimens are associated with a better survival in COVID-19 patients (therapeutic dosages at a higher extent than prophylactic), particularly in ICU patients. However, due to the higher risk of bleeding at therapeutic doses, in noncritically ill COVID-19 patients, the use of prophylactic dosages of anticoagulant is probably to be preferred.

Therefore, while waiting for definitive answers from the ongoing clinical trials, it is important, especially in this period of spread resurgence of the pandemic, to pay attention to the type and dosage of anticoagulant used in the management of hospitalized COVID-19 patients. Randomized controlled clinical trials will be necessary before any conclusion can be reached regarding a potential benefit of these drugs in patients with COVID-19.

Authors' Contributions
S.C. and L.I. contributed to the conception and design of the work and interpretation of data; R.P., S.C., and A.D.C. managed study selection and data extraction and critically reviewed the results; R.P. analyzed the data; R.P. and S.C. wrote the paper; L.I., G.d.G., and M.B.D. originally inspired the research and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Conflict of Interest
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