THERAPEUTIC ADVANCES in
Neurological Disorders

Original Research

Effects of low molecular weight heparin and fondaparinux on mortality, hemorrhagic and thrombotic complications in COVID-19 patients

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is associated with increased thrombosis prevalence. However, there are insufficient data supporting the appropriate anticoagulation dose in COVID-19.

Objective: We aim to systematically assess the currently available data regarding the effects of different dosing regimens of low molecular weight heparin and/or fondaparinux (LMWH/F) on mortality risk as well as the risk of arterial/venous thrombotic events and hemorrhagic complications in confirmed COVID-19 cases.

Design: We conducted a living systematic review and meta-analysis on the effects of different LMWH/F doses on mortality, thrombotic and hemorrhagic events in COVID-19 patients.

Data Sources and Methods: MEDLINE, Scopus, Embase, Cochrane Library, Cochrane COVID-19 study register, European Union Drug Regulating Authorities Clinical Trials Database, and ClinicalTrials.gov were searched to detect observational cohort studies and randomized-controlled clinical trials (RCTs) comparing difference doses of LMWH/F among confirmed COVID-19 cases.

Results: Thirty-one eligible studies (6 RCTs and 25 cohort studies) with 11,430 hospitalized patients were included. No association was found between LMWH/F and mortality during the following comparisons: (1) no LMWH/F versus any LMWH/F; (2) prophylactic versus higher than prophylactic LMWH/F; (3) prophylactic versus therapeutic LMWH/F; (4) intermediate versus therapeutic LMWH/F; and (5) lower than therapeutic versus therapeutic LMWH/F. Mortality was higher in patients receiving prophylactic versus intermediate LMWH/F (OR = 2.01; 95% CI: 1.19–3.39). However, this effect was mostly driven by observational data. No associations were detected between the intensity of LMWH/F and the risk of thrombotic and hemorrhagic events, except the lower risk for hemorrhage in patients on prophylactic compared to higher LMWH/F doses.

Conclusion: The risk for all-cause mortality was higher in patients receiving prophylactic LMWH/F compared to those on an intermediate dose of LMWH/F, based on observational data. These results should be interpreted in light of the moderate quality and heterogeneity of the included studies.

Registration: The study protocol has been registered in the International Prospective Register of Ongoing Systematic Reviews PROSPERO (Registration number: CRD42021229771).

Keywords: COVID-19, fondaparinux, low molecular weight heparin, mortality, SARS-CoV-2

Received: 15 June 2021; revised manuscript accepted: 20 April 2022.

Introduction

As the coronavirus disease 2019 (COVID-19) pandemic continues to evolve globally, our understanding of the underlying pathogenetic mechanisms still remains largely obscure. However, an increasing body of data supports

Ther Adv Neurol Disord

2022, Vol. 15: 1–17

DOI: 10.1177/17562864221099472

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that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and—most importantly—its progression to severe and critical COVID-19 disease, may be attributed to the widespread endothelial cell damage either directly by the virus itself, or indirectly by the burst of proinflammatory cytokines, as well as the activation of complement and the development of systemic microangiopathy that leads to multi-organ damage.[1]

The loss of endothelial integrity (endotheliopathy) and, consequently, the destruction of the vascular wall homeostasis are associated with a procoagulant state that activates and propagates intravascular coagulation, and leads to an increased prevalence of arterial and venous thrombotic complications in severely and critically ill COVID-19 patients.[1] The procoagulant state in COVID-19 patients is evident not only through abnormal coagulation profiles[2]—that are routinely used in most laboratories worldwide—but also through more sophisticated tests. Indeed, a study by Ranucci *et al.*[3] in patients with COVID-19-induced acute respiratory distress syndrome demonstrated an increased clot strength with platelet and fibrinogen contribution, using point-of-care viscoelastic tests, thus strengthening the hypothesis of activation of intravascular coagulation mechanism and verifying the hypercoagulability seen in COVID-19 infection. The prevalence of both arterial and venous thrombotic events in COVID-19 cases has been reported to range between 5.2% and 30% among different studies,[4–7] although the overall risk of stroke among hospitalized patients with SARS-CoV-2 infection was found as low as 0.5% in a large multi-center observational study.[7]

Taking these observations into consideration, the international stakeholders and organizations have issued guidelines on the use of antithrombotic agents in hospitalized COVID-19 patients; the National Institutes of Health of the USA and the American Society of Hematology recommend the use of prophylactic anticoagulation in all non-pregnant hospitalized adults (unless contraindicated) and suggest the administration of therapeutic doses when thrombosis is proved or highly suspected on a clinical basis.[8,9] However, there are currently insufficient data supporting the use of intermediate or high (therapeutic) anticoagulation dose outside this context.[8] In addition, the effects of no anticoagulation *versus* anticoagulation and the different antithrombotic dosing schemes on mortality remain unknown.

To address these questions, we conducted a living systematic review and meta-analysis of studies comparing the mortality of patients with laboratory-confirmed COVID-19 disease not receiving any anticoagulation *versus* those who were anticoagulated with low molecular weight heparin or fondaparinux (LMWH/F); furthermore, we compared the mortality of patients under LMWH/F at a standard thromboprophylaxis dose *versus* intermediate or therapeutic dose. Finally, we explored the risk of hemorrhagic and thrombotic events among the aforementioned COVID-19 patient subgroups.

Methods

Search strategy, study selection, and data extraction

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines 2020.[10] The study protocol was established *a priori* and has been registered in the International Prospective Register of Ongoing Systematic Reviews PROSPERO (Registration number: CRD42021229771). Our study did not require an ethical board approval or written informed consent by the patients according to the study design (systematic review and meta-analysis).

A systematic literature search was conducted to identify eligible studies published in MEDLINE, Scopus, Embase, Cochrane Library, Cochrane COVID-19 study register, EudraCT (European Union Drug Regulating Authorities Clinical Trials Database), and ClinicalTrials.gov, between 30 December 2019 (the day of declaration of the first COVID-19 case) to 28 November 2021. The combination of search strings applied to query all databases included the following: 'low molecular weight heparin', 'dalteparin', 'enoxaparin', 'nadroparin', 'tinzaparin', 'fondaparinux', 'heparin', 'antithrombotic', 'anticoagulant', and 'COVID-19', 'SARS-CoV-2', or 'coronavirus'. The respective algorithms for each database search are available in the online Supplement. Database interrogation was performed by three independent researchers (PCF, LP, and MIS), who additionally searched manually conference abstracts and reference lists of

published articles to ensure the comprehensiveness of bibliography.

All observational studies (prospective or retrospective) and randomized-controlled clinical trials (RCTs) that provided data on mortality, thrombotic and/or hemorrhagic events in COVID-19 patients undergoing anticoagulation with LMWH/F at any dose (as standard thromboprophylaxis, intermediate or therapeutic dose) were identified.

Eligible studies were included using the following criteria: (1) studies including patients of any age, (2) with COVID-19 diagnosis confirmed by a positive molecular test of any severity (the criteria for confirmed COVID-19 are shown in Supplementary Table 1), (3) who received LMWH/*F* at any dose and contemporary COVID-19 controls who underwent a different dosing scheme of LMWH/F (including no anticoagulation), and (4) reported data on the outcomes of interest.

We excluded studies: (1) including suspected or probable COVID-19 cases (case definitions are shown in Supplemental Table 1); (2) without control population; and (3) reporting interventions not aligned with our pre-defined inclusion criteria, including treatment with classic (unfractionated) heparin, other parenteral or oral anticoagulants. Non-English publications, case reports, case series with <10 patients, commentaries, narrative and systematic reviews, non-peer reviewed studies, and pre-prints were also excluded from further analyses.

In case of overlapping data between studies, the study with the largest dataset was retained. Independent assessment of retrieved studies was performed based on the previous inclusion/exclusion criteria by three reviewers (PCF, LP, and MIS), and any disagreements were resolved by the senior author (GT).

Data extraction was performed by three independent reviewers (PCF, LP, and MIS). We extracted data regarding study details (type of study, dates of recruitment, location, publication year, etc.), baseline characteristics of each study's population (mean age, number of males, COVID-19 severity and setting of treatment, co-morbidities), and details on the outcomes of interest (type and dose of anticoagulation, mortality rate number and type of thrombotic and hemorrhagic events for each group of different treatments). Potential disagreements in data abstraction were resolved by the senior author (GT).

An aggregate data meta-analysis was performed including observational studies and RCTs reporting on rates of all-cause mortality, thrombotic or hemorrhagic events in COVID-19 patients undergoing anticoagulation with LMWH/F *versus* contemporary COVID-19 controls as previously defined.

Plan for establishing living evidence

We plan to update our results with emerging evidence arising from new observational studies or RCTs, by following the same search method as described in our protocol every four months. The reviewers who did the initial search (PCF, LP, and MIS) will evaluate the new evidence according to the pre-defined inclusion and exclusion criteria, and we will meta-analyze the new data according to our pre-defined methods.

Study quality control and risk of bias assessment

Eligible studies were subjected to quality control and bias assessment employing the Cochrane Collaboration toll (RoB 2)[11] for RCTs and the Newcastle-Ottawa Scale[12] for cohort studies. The quality control and risk of bias assessment was conducted independently by three reviewers (PCF, LP, and MIS), and disagreements were resolved *via* consensus after discussion with the senior author (GT).

Outcomes

Our pre-defined primary outcome measure was all-cause mortality of COVID-19 patients under no anticoagulation *versus* LMWH/F at any dose. Secondary outcomes comprised: (1) thrombotic events (including venous thromboembolism, pulmonary thromboembolism, deep vein thrombosis, ischemic stroke, and myocardial infarction), and (2) hemorrhagic events (including intracerebral hemorrhage and hemorrhagic complications of any type) in COVID-19 patients under no anticoagulation *versus* those under different doses of LMWH/F. The same outcomes were also assessed in COVID-19 patients receiving: (1) prophylactic *versus* higher than prophylactic LMWH/F dose (i.e., intermediate or therapeutic); (2) prophylactic *versus* therapeutic LMWH/F; (3) prophylactic *versus* intermediate LMWH/F; (4) intermediate *versus* therapeutic LMWH/*F*; and (5) lower than therapeutic LMWH/F (i.e., intermediate or prophylactic) *versus* therapeutic LMWH/F.

We evaluated for potential differences in demographics between groups of COVID-19 patients stratified by anticoagulation status. We also assessed the previous outcomes of interest in subgroup analyses after stratification according to the treatment setting of COVID-19 (i.e., outpatient, inpatient medical ward or ICU). Finally, we performed a secondary analysis to assess for potential differences between study designs (RCTs *versus* observational studies).

Statistical analysis and measures of effects

In the current meta-analysis, the aforementioned outcomes of interest were dichotomous variables. The random-effects model of meta-analysis (DerSimonian and Laird)[13] was used to estimate individual study effects for each association. The random-effect model, since a different underlying true effect was assumed for each study and we aimed to provide more generalizable hypotheses for the population.[13,14] Pairwise comparisons between COVID-19 patients with LMWH/F and COVID-19 controls (according to the pre-defined between-group comparisons based on LMWH/F dose) are reported using odds ratios (ORs) and corresponding 95% confidence intervals (95% CI), as measures of effects.

As per the Cochrane Handbook for Systematic Reviews of Interventions,[15] heterogeneity between included studies was assessed using the Cochran Q and I^2 statistics. For the qualitative interpretation of heterogeneity, I^2 values $>50\%$ and values $>75\%$ were considered to represent substantial and considerable heterogeneity, respectively.[15] The significance level for the Q statistic was set at 0.1.

Publication bias across individual studies was graphically assessed for the primary outcome, when more than five studies were included in each analysis, using both funnel plot inspection and the Egger's linear regression test,[16] and the equivalent z-test for each pooled estimate with a two-tailed p value <0.05 was considered statistically significant.

All statistical analyses were performed using the Cochrane Collaboration's Review Manager (RevMan 5.3) Software Package (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014), the Open MetaAnalyst[17] and R software version 3.5.0 (package: metafor).

Results

Literature search and included studies

The records retrieved by the systematic search in each electronic database are shown in Figure 1. After excluding duplicates and out-of-scope articles based on title/abstract, 349 potentially eligible records for inclusion were selected for full-text reading. After full-text reading, 318 articles were excluded, leading to the inclusion of 31 eligible studies[18–48] (6 RCTs and 25 cohort studies) with a total of 11,430 COVID-19 patients (Table 1). Only hospitalized patients were included in these studies.

Quality control of included studies and risk of bias assessment

The risk of bias in included RCTs was assessed by the Cochrane Collaboration tool (RoB 2)[11] and is shown in Supplementary Figures S1 and S2. Overall, the included RCTs presented low risk of bias in most individual domains, with the exception of high risk of performance and detection bias, since blinding was not achieved in the majority of the studies. The risk of bias of the included observational studies was assessed by the Newcastle-Ottawa scale[12] (Supplementary Table S2). The overall score was 194 of 225 (86%), which is indicative of moderate quality. Funnel plot inspection revealed low risk of publication bias, with the exception of the comparison of prophylactic *versus* intermediate LMWH/F, which presented evidence of publication bias, possibly due to small study effects (Supplementary Figures S3–S7).

Demographics of study population

The mean age of included COVID-19 patients was 63.40 years (95% CI: 59.78–67.03; 23 studies; $I^2=99.1\%$; p for Cochran $Q<0.0001$; Supplementary Figure S8). No clinically significant difference in mean age was identified between COVID-19 patients receiving: a) no anticoagulation *versus* any LMWH/*F* (mean difference (MD) = –0.49; 95% CI: –4.02, 3.05; 4 studies; $I^2=87\%$; p for Cochran $Q<0.0001$; Supplementary Figure S9); b) prophylactic *versus* higher than prophylactic LMWH/*F* (MD = 0.22; 95% CI: –0.96, 1.39; 14 studies; $I^2=30\%$; p for Cochran $Q=0.14$; Supplementary Figure S10); c) prophylactic *versus* therapeutic LMWH/*F* (MD = –2.16; 95% CI: –4.18, –0.15); 6 studies; $I^2=21\%$; p for Cochran

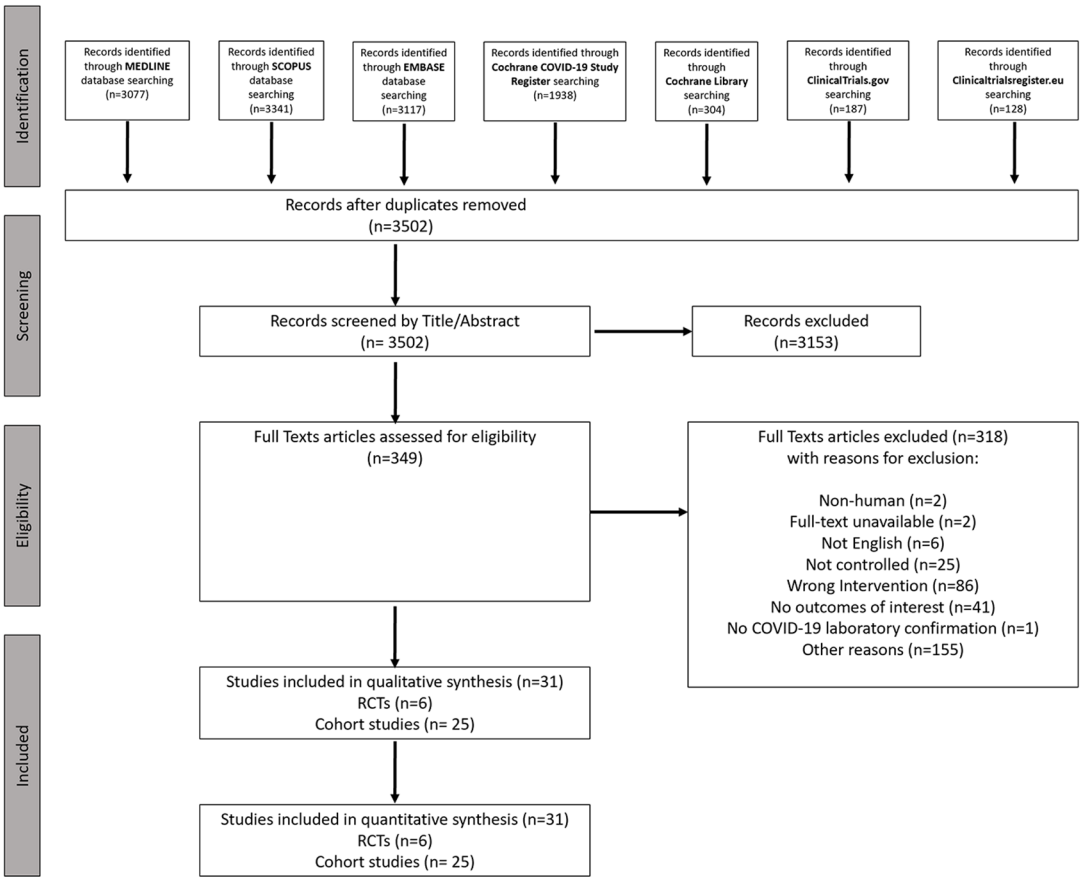

Figure 1. Systematic review flow chart.

$Q = 0.27$; Supplementary Figure S11); d) prophylactic *versus* intermediate LMWH/*F* (MD = 1.50; 95% CI:–0.43, 3.42; 9 studies; $I^2 = 49\%$; p for Cochran $Q = 0.05$; Supplementary Figure-S12); e) intermediate *versus* therapeutic LMWH/*F* (MD = –4.40; 95% CI: –8.43,0.37; 4 studies; $I^2 = 68\%$; p for Cochran $Q = 0.02$; Supplementary Figure S13); and f) lower than therapeutic *versus* therapeutic LMWH/*F* (MD = –1.69; 95% CI: –4.11,0.73; 7 studies; $I^2 = 58\%$; p for Cochran $Q = 0.03$; Supplementary Figure S14). The pooled proportion of men out of the total population included in this meta-analysis was 60.6% (95% CI: 56.7–64.5%), with no sex differences noted, stratified by different LMWH/F dosing schemes (Supplementary Figures S15–S21).

Effects on mortality

A summary of findings is shown in Table 2. No association between LMHW/F administration and mortality was detected in COVID-19 patients without anticoagulation *versus* any LMWH/*F* (OR = 0.98; 95% CI: 0.42–2.28; 6 studies; $I^2 = 95\%$; p for Cochran Q: < 0.00001; Figure 2), with the limitation that only 6 studies with significant heterogeneity between reported outcomes were identified. There was also no difference in mortality among patients treated with prophylactic LMWH/F *versus* higher than prophylactic LMWH/*F* (OR = 1.28; 95% CI: 0.84–1.94; 16 studies; $I^2 = 78\%$; p for Cochran $Q < 0.00001$; Supplementary Figure S22) or among patients treated with prophylactic *versus* therapeutic LMWH/*F* (OR = 0.82; 95% CI: 0.39–1.76; 9 studies; $I^2 = 83\%$; p for Cochran $Q < 0.00001$; Supplementary Figure S23). Conversely, the risk for all-cause mortality was higher in patients receiving prophylactic *versus* intermediate LMWH/*F* (OR = 2.01; 95% CI: 1.19–3.39; 8 studies; $I^2 = 68\%$; p for Cochran $Q = 0.002$; Figure 3). The corresponding mortality rates were comparable between patients undergoing intermediate compared with therapeutic LMWH/*F* (OR = 0.60; 95% CI:

Table 1. Characteristics of included studies.

First author (Ref.)	Study location	Study period	Study design	Setting of population of interest	N of COVID-19 patients	Outcomes of interest	Type of anticoagulation	LMWH/F dose		
								Prophylactic	Intermediate	Therapeutic
Randomized-controlled trials										
ACTION[18]	Brazil	24 June 2020 to 26 February 2021	RCT	ICU or medical ward	285	All Hemorrhagic Events	LMWH	⊕	⊖	⊕
BEMICOP[21]	Spain	October 2020 to May 2021	RCT	Medical ward	65	Mortality	LMWH	⊕	⊖	⊕
HEP-COVID[30]	US	8 May 2020 to 14 May 2021	RCT	ICU or medical ward	253	Mortality; VTE; PE; DVT; IS; MI; All Hemorrhagic Events	LMWH	⊕	⊕	⊕
INSPIRATION[31]	Iran	29 July to 19 November 2020	RCT	ICU	562	Mortality; VTE; IS; MI; ICH; All Hemorrhagic Events	LMWH	⊕	⊕	⊖
Oliynyk *et al.*[38]	Ukraine	1 July 2020 to 1 March 2021	RCT	ICU	84	Mortality	LMWH	⊕	⊖	⊕
Perepu *et al.*[42]	US	26 April 2020 to 6 January 2021	RCT	ICU or medical ward	173	Mortality; VTE; IS; MI; All Hemorrhagic Events	LMWH	⊕	⊕	⊖
Observational studies										
Albani *et al.*[19]	Italy	20 February to 10 May 2020	Retrospective cohort	ICU or medical ward	1403	Mortality: VTE; PE; IS; MI; All Hemorrhagic Events	LMWH	⊕	⊖	⊕
Avruscio *et al.*[20]	Italy	4 March to 30 April 2020	Prospective cohort	ICU or medical ward	85	VTE	LMWH/F	⊕	⊖	⊕
Canoglu *et al.*[22]	Turkey	11 March to 30 April 2020	Retrospective cohort	ICU or medical ward	154	Mortality	LMWH	⊕	⊖	⊕
Copur *et al.*[23]	Turkey	11 March to 11 April 2020	Retrospective cohort	Medical ward	115	Mortality	LMWH	⊕	⊖	⊕
Elmelhat *et al.*[24]	Dubai	March–June 2020	Retrospective cohort	ICU or medical ward	59	Mortality; ICH; All Hemorrhagic Events	LMWH	⊕	⊖	⊕
Espallargas *et al.*[25]	Spain	18 March to 11 April 2020	Retrospective cohort	ICU or medical ward	47	PE	LMWH	⊕	⊕	⊕
Falcone *et al.*[26]	Italy	4 March to 30 April 2020	Prospective cohort	ICU or medical ward	315	Mortality: ICH; All Hemorrhagic Events	LMWH	⊕	⊖	⊕
Gonzalez-Porras *et al.*[27]	Spain	1 March to 7 April 2020	Retrospective cohort	Medical ward	690	Mortality; PE; DVT; IS; MI; ICH; All Hemorrhagic Events	LMWH	⊕	⊕	⊕
Grandone *et al.*[28]	Italy	03 March to 30 August 2020	Retrospective cohort	ICU or medical ward	264	All Hemorrhagic Events	LMWH	⊕	⊕	⊕
Hamilton *et al.*[29]	UK	31 March to 16 November 2021	Retrospective cohort	ICU	58	PE	LMWH	⊕	⊕	⊖

(Continued)

Table 1. (Continued)

First author (Ref.)	Study location	Study period	Study design	Setting of population of interest	N of COVID-19 patients	Outcomes of interest	Type of anticoagulation	LMWH/F dose		
								Prophylactic	Intermediate	Therapeutic
Jimenez-Guiu *et al.*[32]	Spain	April 2020	Prospective cohort	Medical ward	57	DVT; All Hemorrhagic Events	LMWH	⊕	⊕	⊕
Jiménez-Soto *et al.*[33]	Mexico	12 March to 15 July 2020	Retrospective cohort	ICU or medical ward	321	Mortality; PE; All Hemorrhagic Events	LMWH	⊕	⊕	⊕
Jonmarker *et al.*[34]	Sweden	March to April 2020	Retrospective cohort	ICU	152	Mortality; VTE; PE; DVT; IS; ICH; All Hemorrhagic Events	LMWH	⊕	⊕	⊕
Martinelli *et al.*[35]	Italy	9 March to 7 April 2020	Retrospective cohort	ICU or medical ward	278	Mortality; VTE: PE; DVT; ICH; All Hemorrhagic Events	LMWH	⊕	⊖	⊖
Mennuni *et al.*[36]	Italy	20 February to 12 May 2020	Retrospective cohort	ICU or medical ward	436	Mortality: VTE; All Hemorrhagic Events	LMWH	⊕	⊕	⊕
Nadkarni *et al.*[37]	USA	1 March to 30 April 2020	Retrospective cohort	ICU or medical ward	2202	All Hemorrhagic Events	LMWH	⊕	⊖	⊕
Paolisso *et al.*[39]	Italy	1 March to 10 April 2020	Retrospective cohort	ICU or medical ward	450	Mortality; IS; MI; ICH; All Hemorrhagic Events	LMWH	⊕	⊕	⊖
Pavoni *et al.*[40]	Italy	NR	Retrospective cohort	ICU	42	Mortality; PE; DVT	LMWH	⊖	⊕	⊕
Perazzo *et al.*[41]	Italy	March to April 2020	Retrospective cohort	Medical ward	16	Mortality	LMWH	⊕	⊕	⊖
Pieralli *et al.*[43]	Italy	21 March to 25 May 2020	Prospective cohort	Medical ward	222	DVT	LMWH/F	⊕	⊕	⊕
Qin *et al.*[44]	China	10 Jan to 28 Feb 2020	Retrospective cohort	ICU or medical ward	749	Mortality; All Hemorrhagic Events	LMWH	⊕	⊖	⊕
Shen *et al.*[45]	China	26 January to 26 March 2020	Retrospective cohort	ICU or medical ward	525	Mortality: ICH; All Hemorrhagic Events	LMWH	⊕	⊖	⊕
Stessel *et al.*[46]	Belgium	13 March to 20 April 2020	Retrospective cohort	ICU	72	Mortality; VTE; ICH; All Hemorrhagic Events	LMWH	⊕	⊕	⊖
Trigonis *et al.*[47]	USA	23 March to 8 April 2020	Retrospective cohort	ICU	45	DVT	LMWH	⊕	⊕	⊖
Ugur *et al.*[48]	Turkey	12 March to 17 April 2020	Retrospective cohort	Medical ward	1251	Mortality	LMWH	⊕	⊕	⊕

DVT: deep vein thrombosis; ICH: intracranial hemorrhage; ICU: intensive care unit; IS: ischemic stroke; LMWH: low molecular weight heparin; LMWH/F: low molecular weight heparin or fondaparinux; MI: myocardial infarction; NR: not reported; PE: pulmonary embolism; and VTE: venous thromboembolism.

Table 2. Summary of findings on mortality, thrombotic and hemorrhagic events analyses.

Outcome	No Anticoagulation *versus* Any LMWH/F			Prophylactic LMWH/F *versus* Higher than Prophylactic LMWH/F			Prophylactic LMWH/F *versus* Therapeutic LMWH/F	
	N of studies	Odds ratio (95% CI)	I^2, p (CQT)	N of studies	Odds ratio (95% CI)	I^2, *p* (CQT)	N of studies	Odds ratio (95% CI)
Mortality	6	0.98 (0.42–2.28)	95%, < 0.00001	16	1.28 (0.84–1.94)	78%, <0.00001	9	0.82 (0.39–1.76)
Thrombotic events								
Venous thromboembolism	–	–	–	8	0.67 (0.30–1.47)	78%, <0.0001	3	0.59 (0.06–6.01)
Pulmonary embolism	–	–	–	7	0.55 (0.18–1.70)	73%, 0.001	5	0.62 (0.11–3.68)
Deep vein thrombosis	–	–	–	6	1.24 (0.73–2.11)	0%, 0.48	3	2.09 (0.35–12.36)
Ischemic stroke	–	–	–	6	1.03 (0.37–2.91)	0%, 0.44	3	1.22 (0.33–4.50)
Myocardial infarction	–	–	–	5	0.59 (0.24–1.45)	0%, 0.41	–	–
Hemorrhagic events								
Intracranial hemorrhage	–	–	–	9	0.74 (0.08–6.98)	34%, 0.22	–	–
Any hemorrhage	7	0.57 (0.25–1.28)	53%, 0.05	16	0.37 (0.21–0.64)	54%, 0.005	10	0.30 (0.14–0.64)

CI: confidence interval; CQT: Cochran's *Q* test; and LMWH/F, low molecular weight heparin or fondaparinux.

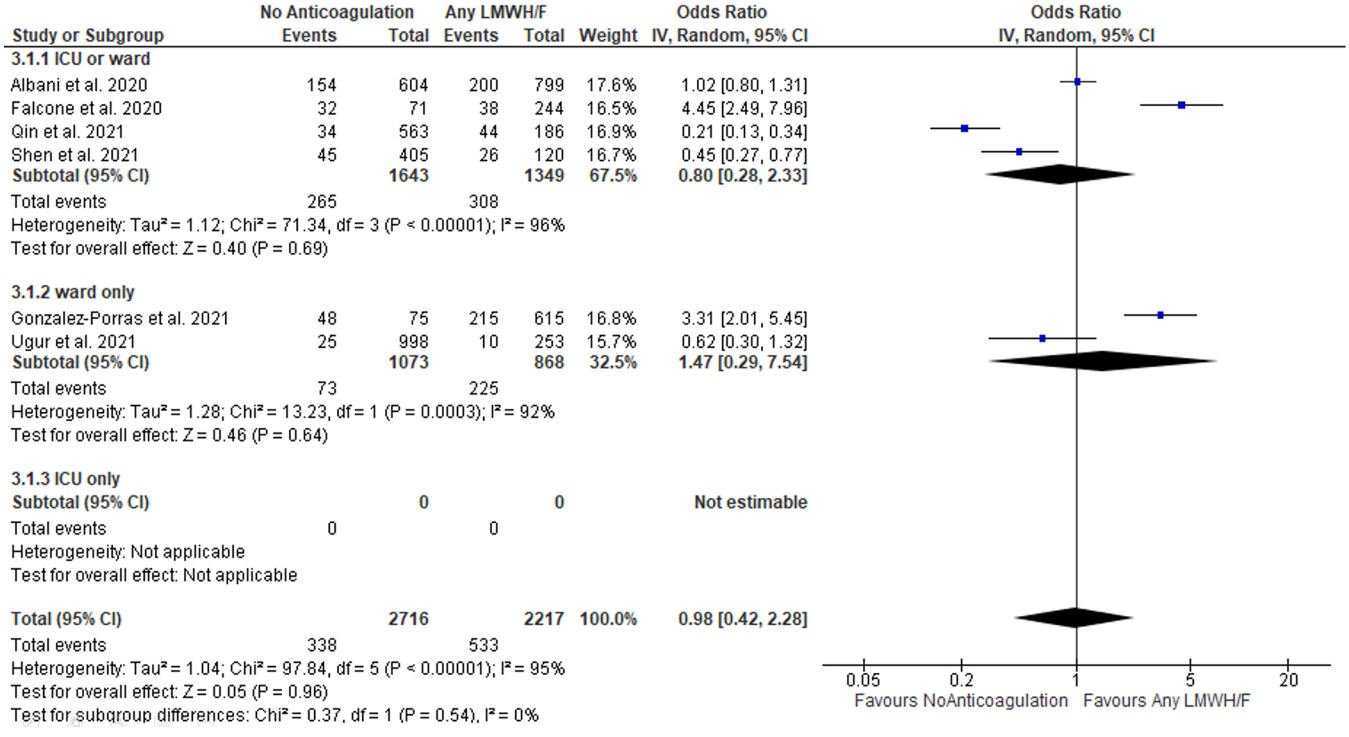

Figure 2. Forest plot presenting the odds ratio for all-cause mortality between patients treated with no *versus* any anticoagulation with low molecular weight heparin and/or fondaparinux.

Table 2. (Continued)

	Prophylactic LMWH/F *versus* Intermediate LMWH/F			Intermediate LMWH/F *versus* Therapeutic LMWH/F			Lower than Therapeutic *versus* Therapeutic LMWH/F		
I^2, p (CQT)	N of studies	Odds ratio (95% CI)	I^2, p (CQT)	N of studies	Odds ratio (95% CI)	I^2, p (CQT)	N of studies	Odds ratio (95% CI)	I^2, p (CQT)
83%, <0.00001	8	2.01 (1.19–3.39)	68%, 0.002	4	0.60 (0.26–1.41)	55%, 0.08	11	0.79 (0.42–1.47)	80%, < 0.00001
83%, 0.003	4	1.24 (0.66–2.35)	32%, 0.22	–	–	–	3	1.07 (0.08–14.21)	88%, 0.0003
77%, 0.002	5	0.79 (0.31–2.00)	38%, 0.17	5	1.49 (0.49–4.54)	15%, 0.32	7	0.78 (0.20–3.10)	77%, 0.0002
0%, 0.91	5	1.14 (0.42–3.07)	29%, 0.23	3	1.01 (0.05–22.19)	76%, 0.01	4	2.77 (1.32–5.80)	0%, 0.99
0%, 0.37	5	0.87 (0.23–3.33)	0%, 0.49	–	–	–	4	1.05 (0.32–3.41)	0%, 0.65
–	4	0.54 (0.08–3.67)	52%, 0.12	–	–	–	3	1.02 (0.19–5.31)	37%, 0.21
–	5	0.45 (0.05–4.51)	37%, 0.20	–	–	–	3	1.12 (0.12–10.25)	0%, 0.72
56%, 0.01	8	0.63 (0.32–1.24)	49%, 0.06	2	0.50 (0.03–8.20)	88%, 0.003	11	0.30 (0.15–0.62)	57%, 0.01

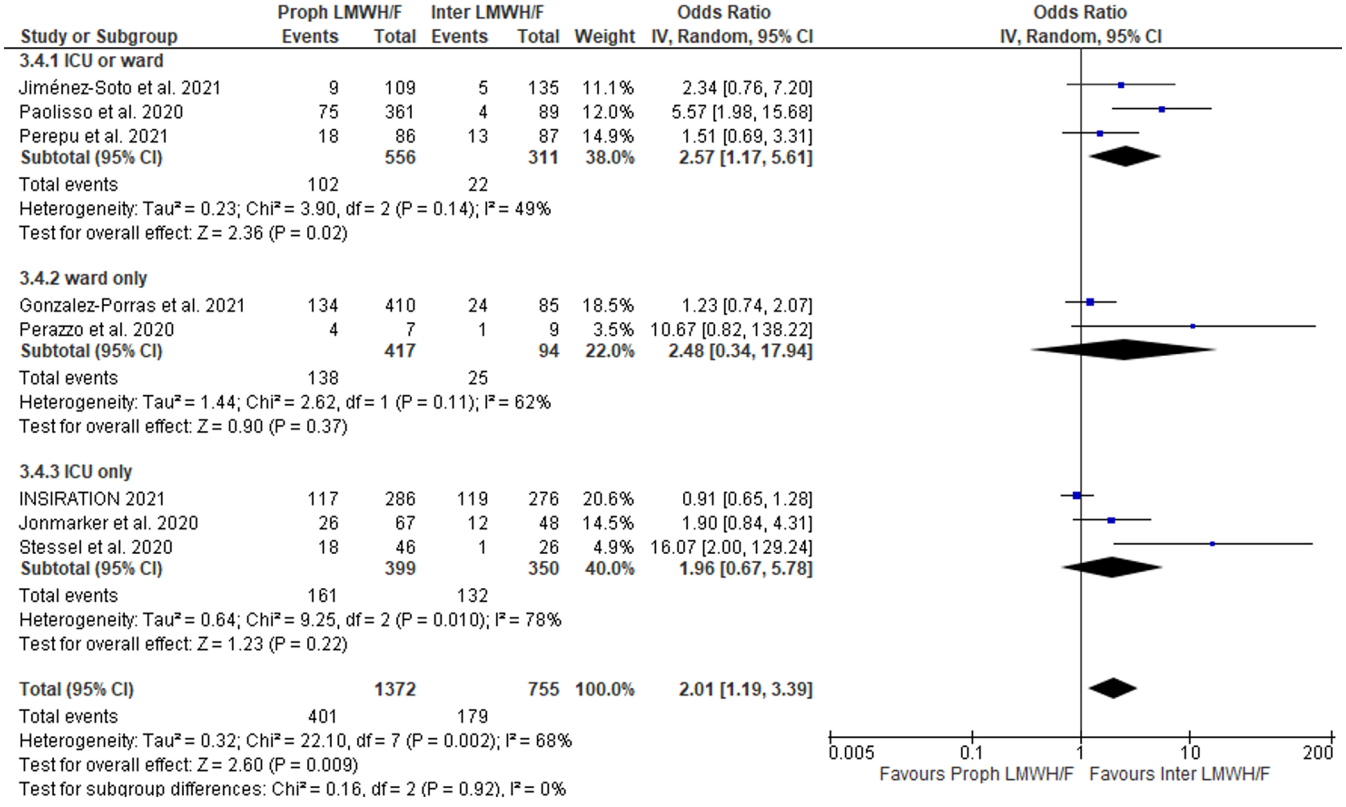

Figure 3. Forest plot presenting the odds ratio for all-cause mortality between patients who received prophylactic *versus* intermediate anticoagulation with low molecular weight heparin and/or fondaparinux.

0.26–1.41; 4 studies; I^2=55%; p for Cochran Q=0.08; Supplementary Figure S24), as well as between patients treated with lower than therapeutic *versus* therapeutic LMWH/*F* (OR=0.79; 95% CI: 0.42–1.47; 11 studies; I^2=80%; p for Cochran Q<0.00001; Supplementary Figure S25).

Effects on thrombotic events

Concerning thrombotic events in COVID-19 patients, no association was found between intensity of LMWH/F and risk of venous thromboembolism (VTE), defined as the composite of deep vein thrombosis or pulmonary embolism, in patients receiving: a) prophylactic compared to higher than prophylactic LMWH/*F* (OR=0.67; 95% CI: 0.30–1.47; 8 studies; I^2=78%; p for Cochran Q<0.0001; Figure 4); b) prophylactic compared to therapeutic LMWH/*F* (OR=0.59; 95% CI: 0.06–6.01; 3 studies; I^2=83%; p for Cochran Q=0.003; Supplementary Figure S26); c) prophylactic compared to intermediate LMWH/*F* (OR=1.24; 95% CI: 0.66–2.35; 4 studies; I^2=32%; p for Cochran Q=0.22; Supplementary Figure S27); and d) lower than therapeutic *versus* therapeutic LMWH/*F* (OR=1.07; 95% CI: 0.08–14.21; 3 studies; I^2=88%; p for Cochran Q=0.0003; Supplementary Figure S28).

Similarly, the odds for pulmonary embolism (PE) were comparable between patients receiving: a) prophylactic compared to higher than prophylactic LMWH/*F* (OR=0.55; 95% CI: 0.18–1.70; 7 studies; I^2=73%; p for Cochran Q=0.001; Supplementary Figure S29); b) prophylactic compared to therapeutic LMWH/*F* (OR=0.62; 95% CI: 0.11–3.68; 5 studies; I^2=77%; p for Cochran Q=0.002; Supplementary Figure S30); c) prophylactic compared to intermediate LMWH/*F* (OR=0.79; 95% CI: 0.31–2.00; 5 studies; I^2=38%; p for Cochran Q=0.17; Supplementary Figure S31); d) intermediate *versus* therapeutic LMWH/*F* (OR=1.49; 95% CI: 0.49–4.54; 5 studies; I^2=15%; p for Cochran Q=0.32; Supplementary Figure S32); and e) lower than therapeutic compared to therapeutic LMWH/*F* (OR=0.78; 95% CI: 0.20–3.10; 7 studies; I^2=77%; p for Cochran Q=0.0002; Supplementary Figure S33).

Regarding deep vein thrombosis (DVT), we detected no associations between the intensity of anticoagulation and the risk for DVT in patients receiving: a) prophylactic *versus* higher than prophylactic LMWH/*F* (OR: 1.24; 95% CI 0.73–2.11; 6 studies; I^2 0%; p for Cochran Q=0.48; Supplementary Figure S34); b) prophylactic *versus* therapeutic LMWH/*F* (OR: 2.09; 95% CI 0.35–12.36; 3 studies; I^2 0%; p for Cochran Q=0.91; Supplementary Figure S35); c) prophylactic *versus* intermediate LMWH/*F* (OR 1.14; 95% CI 0.42–3.07; 5 studies; I^2 29%; p for Cochran Q=0.23; Supplementary Figure S36); and d) intermediate *versus* therapeutic LMWH/*F* (OR: 1.01; 95% CI 0.05–22.19; 3 studies; I^2 76%; p for Cochran Q=0.01; Supplementary Figure S37). When lower than therapeutic LMWH/F was compared to therapeutic LMWH/F, a higher rate of DVT was recorded in the lower-than-therapeutic LMWH/F group (OR=2.77; 95% CI: 1.32–5.80; 4 studies; I^2=0%; p for Cochran Q=0.99; Supplementary Figure S38), which was mostly driven by the results of HEP-COVID.[30]

No increased risk of ischemic stroke was detected in patients receiving: a) prophylactic *versus* higher than prophylactic LMWH/*F* (OR=1.03; 95% CI: 0.37–2.91; 6 studies; I^2=0%; p for Cochran Q=0.44; Supplementary Figure S39); b) prophylactic *versus* therapeutic LMWH/*F* (OR=1.22; 95% CI: 0.33–4.50; 3 studies; I^2=0%; p for Cochran Q=0.37; Supplementary Figure S40); c) prophylactic *versus* intermediate LMWH/*F* (OR=0.87; 95% CI: 0.23–3.33; 5 studies; I^2=0%; p for Cochran Q=0.49; Supplementary Figure S41); and d) lower than therapeutic *versus* therapeutic LMWH/*F* (OR=1.05; 95% CI: 0.32–3.41; 4 studies; I^2=0%; p for Cochran Q=0.65; Supplementary Figure S42).

We detected no associations between the intensity of LMWH/F and the risk for myocardial infarction in patients receiving a) prophylactic *versus* higher than prophylactic LMWH/*F* (OR: 0.59; 95% CI 0.24–1.45; 5 studies; I^2 0%; p for Cochran Q=0.41; Supplementary Figure S43); b) prophylactic *versus* intermediate LMWH/*F* (OR: 0.54; 95% CI 0.08–3.67; 4 studies; I^2 52%; p for Cochran Q=0.12; Supplementary Figure S44); and c) lower than therapeutic *versus* therapeutic LMWH/*F* (OR: 1.02; 95% CI 0.19–5.31; 3 studies; I^2 37%; p for Cochran Q=0.21; Supplementary Figure S45).

Effects on hemorrhagic events

Concerning hemorrhagic events in COVID-19 patients, no associations were detected between

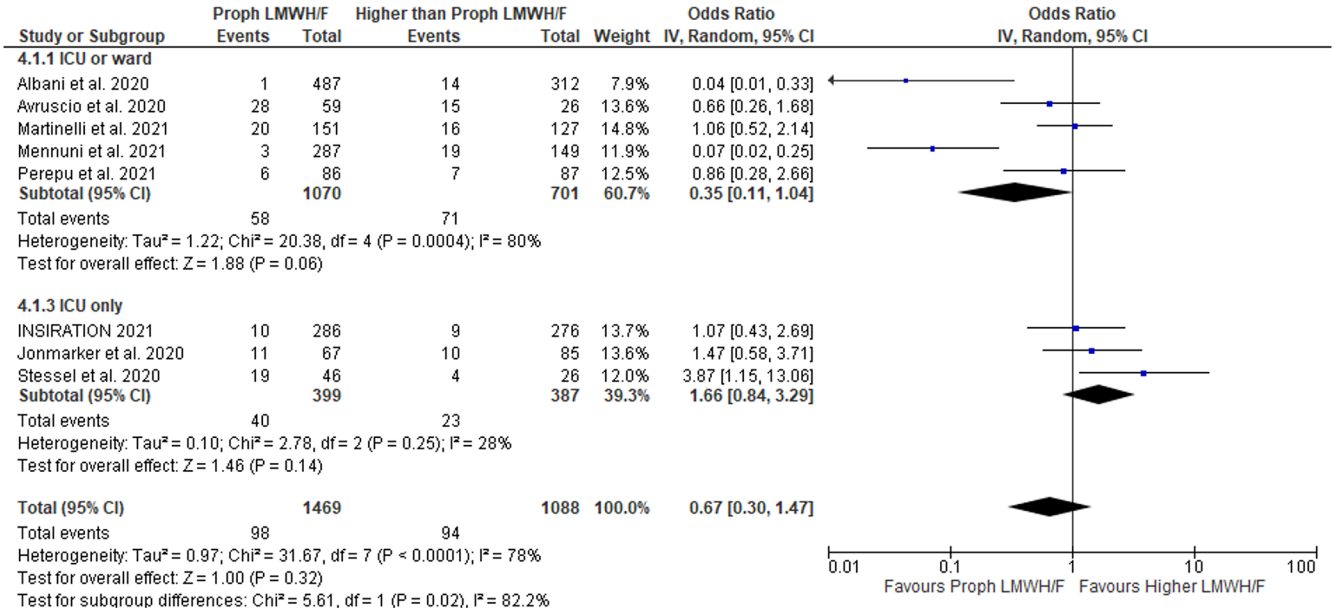

Figure 4. Forest plot presenting the odds ratio for venous thromboembolism between patients who received prophylactic *versus* higher than prophylactic anticoagulation with low molecular weight heparin and/or fondaparinux.

intensity of LMWH/F and the risk for intracerebral hemorrhage (ICH) when comparing: a) prophylactic *versus* higher than prophylactic LMWH/*F* (OR = 0.74; 95% CI: 0.08–6.98; 9 studies; $I^2 = 34\%$; *p* for Cochran $Q = 0.22$; Supplementary Figure S46); b) prophylactic *versus* intermediate LMWH/*F* (OR = 0.45; 95% CI: 0.05–4.51; 5 studies; $I^2 = 37\%$; *p* for Cochran $Q = 0.20$; Supplementary Figure S47); and c) lower than therapeutic *versus* therapeutic LMWH/*F* (OR = 1.12; 95% CI: 0.12–10.25; 3 studies; $I^2 = 0\%$; *p* for Cochran $Q = 0.72$; Supplementary Figure S48).

With respect to the composite outcome of hemorrhagic complications of any type, no differences were noted between patients receiving no anticoagulation *versus* any LMWH/*F* (OR = 0.57; 95% CI: 0.25–1.28; 7 studies; $I^2 = 53\%$; *p* for Cochran $Q = 0.05$; Supplementary Figure S49). However, we found a lower risk for hemorrhagic complications in patients undergoing prophylactic LMWH/*F* compared to higher doses of LMWH/F (OR = 0.37; 95% CI: 0.21–0.64; 16 studies; $I^2 = 54\%$; *p* for Cochran $Q = 0.005$; Figure 5). Similarly, the risk for any hemorrhagic complications was lower in patients treated with prophylactic *versus* therapeutic LMWH/*F* (OR = 0.30; 95% CI: 0.14–0.64; 10 studies; $I^2 = 56\%$; *p* for Cochran $Q = 0.01$; Supplementary Figure S50), but not in patients treated with prophylactic *versus* intermediate LMWH/*F* (OR = 0.63; 95% CI: 0.32–1.24; 8 studies; $I^2 = 49\%$; *p* for Cochran $Q = 0.06$; Supplementary Figure S51) or in patients treated with intermediate *versus* therapeutic LMWH/*F* (OR = 0.50; 95% CI: 0.03–8.20; 3 studies; $I^2 = 88\%$; *p* for Cochran $Q = 0.003$; Supplementary Figure S52). Patients treated with lower than therapeutic compared to therapeutic LMWH/F had a lower likelihood of presenting hemorrhagic complications (OR = 0.30; 95% CI: 0.15–0.62; 11 studies; $I^2 = 57\%$; *p* for Cochran $Q = 0.01$; Supplementary Figure S53).

Secondary analysis

A secondary analysis of the same outcomes of interest (mortality, thrombotic events, and hemorrhagic events) was performed stratifying by different study design (RCTs *versus* observational studies) to assess for potential differences. The results of this analysis are shown in Supplementary Table S3. Significant subgroup differences between study designs were disclosed in the analysis of mortality among patients receiving prophylactic *versus* intermediate LMWH/*F* (*p* for subgroup differences = 0.01; Supplementary Figure S54). The effect of prophylactic compared to intermediate LMWH/F on mortality was mostly driven by observational studies (OR = 2.85;

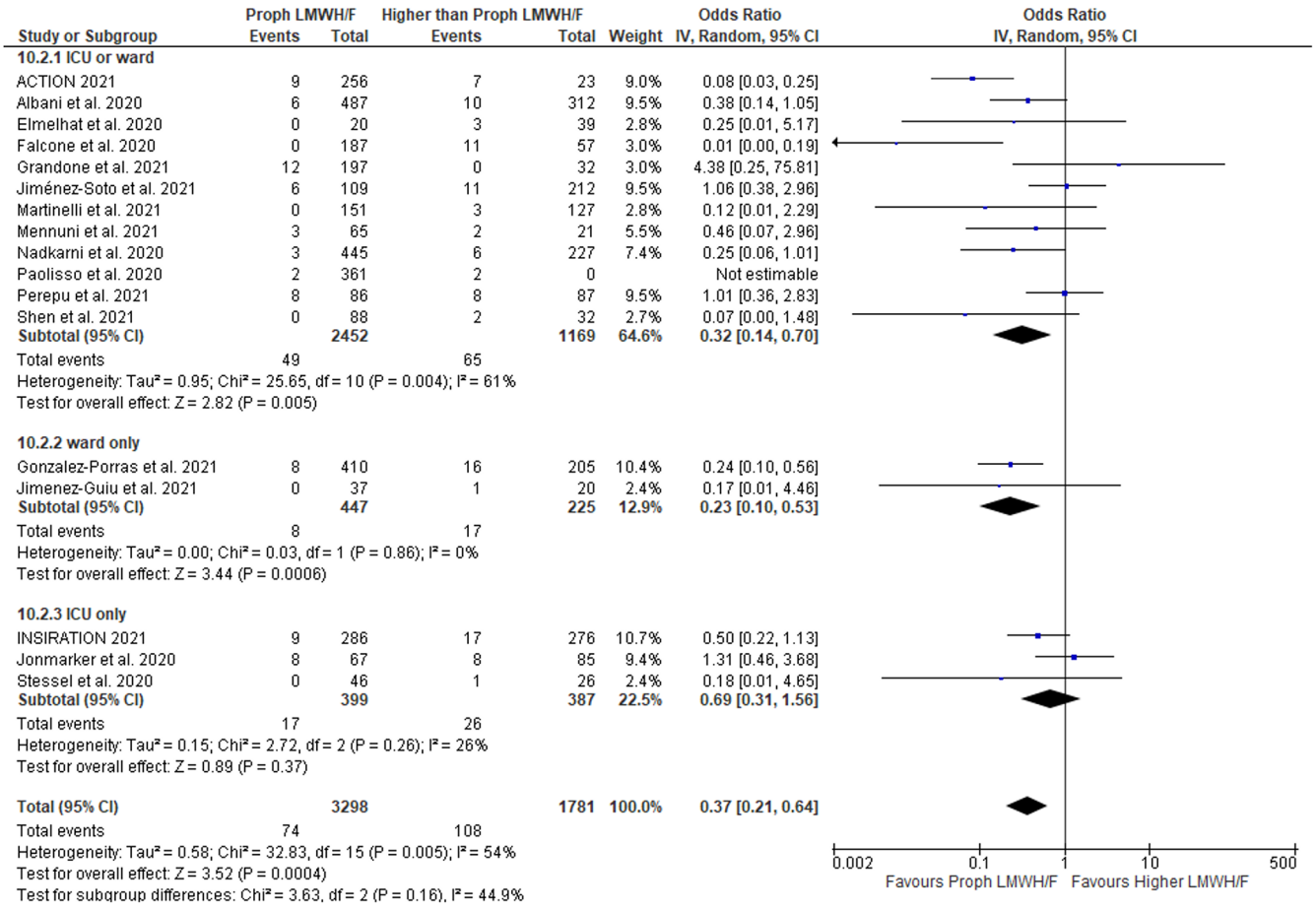

Figure 5. Forest plot presenting the odds ratio for hemorrhagic events between patients who received prophylactic *versus* higher than prophylactic anticoagulation with low molecular weight heparin and/or fondaparinux.

95% CI: 1.41–5.76; 6 studies; $I^2 = 61\%$; p for Cochran $Q = 0.03$), whereas no difference was disclosed when RCTs were evaluated (OR = 1.03; 95% CI: 0.68–1.56; 2 studies; $I^2 = 24\%$; p for Cochran $Q = 0.25$). Significant differences also emerged in the analysis of all hemorrhagic events between patients on prophylactic *versus* therapeutic LMWH/F; however, both subgroups pointed to the same direction (for RCTs: OR = 0.08; 95% CI: 0.03–0.25; 1 study; for observational studies: OR = 0.37; 95% CI: 0.17–0.80; 9 studies; $I^2 = 45\%$; p for Cochran $Q = 0.07$; p for subgroup differences = 0.03; Supplementary Figure S55). No other significant differences between the two subgroups were disclosed.

Discussion

Our living systematic review and meta-analysis provides an overview of the currently available data regarding the effects of different dosing regimens of LMWH/F on mortality risk as well as the risk of arterial/venous thrombotic events and hemorrhagic complications in confirmed COVID-19 cases.

The risk of all-cause mortality was higher in patients receiving prophylactic compared to intermediate doses of LMWH/F. However, this effect was mostly driven by observational data. Similar mortality rates were observed during the comparisons of (a) prophylactic *versus* higher than prophylactic LMWH/F; (b) prophylactic *versus* therapeutic LMWH/F; (c) intermediate *versus* therapeutic LMWH/F; and (*d*) lower than therapeutic *versus* therapeutic LMWH/F. These results may be partly explained by the higher rates of hemorrhagic complications observed in patients treated with higher doses of LMWH/F, whereas the prophylactic doses seem to be equally safe when compared with intermediate LMWH/F.

In addition, no significant difference on mortality risk was identified when we compared populations under no anticoagulation *versus* any dose of LMWH/F. This paradox could be possibly explained by the fact that the majority of the eligible studies included hospitalized patients who often require anticoagulation.[8] In addition, type-II errors cannot be excluded, since in our review, only 6 studies including patients not on anticoagulation were meta-analyzed, while these studies suffered from significant heterogeneity in reported results.[26,45] Thus, no robust conclusions can be drawn for our primary outcome given the paucity of available studies examining the benefits of LMWH/F *versus* no anticoagulation, especially in mild COVID-19 outpatients.

Interestingly, we demonstrated that the risk for all thrombotic events remained similar among the subgroups of different LMWH/F dosing schemes. This phenomenon may indicate that anticoagulants, and especially heparin-derived agents, avail the course of COVID-19 disease through pathophysiologic mechanisms that lie beyond their antithrombotic properties. Indeed, preclinical studies have shown that unfractionated heparin exerts both anti-inflammatory and direct antiviral effects against SARS-CoV-2.[49] Heparin binds irreversibly to the spike-protein (S-protein) as a competitive inhibitor and abrogates the viral entry into the host cells.[49–51] However, shorter-length heparins like the LMWHs have shown lower affinity to S-protein, and therefore, possibly exert little or maybe no direct antiviral effects against SARS-CoV-2, compared to unfractionated heparin.[50] Further studies are needed to explore the antiviral properties of heparin-derived antithrombotics in COVID-19 patients. Besides antiviral activity, it has been repeatedly demonstrated that unfractionated heparin dampens the inflammation in the vasculature and/or respiratory tract by (1) interacting with proinflammatory molecules, (2) neutralizing the extracellular cytotoxic histones, (3) inhibiting the heparanase activity (thus reducing endothelial leakage), and (4) abolishing the adhesion and trafficking of inflammatory cells.[49,52] Therefore, unfractionated heparin and heparin-derived drugs may potentially have pleiotropic beneficial effects on COVID-19 disease, by targeting the activation of coagulation cascade, the hyper-inflammatory response, and the virus itself.[53] This phenomenon, might also explain that effects of anticoagulation were similar in patients hospitalized in the ICU and in non-ICU wards, as observed in our analysis.

With regard to thrombotic events, we found no associations between VTE, DVT, PE, stroke, and myocardial infarction risk with the use or the intensity of LMWH/F administered. This could be possibly explained by the small number and the design of the included studies, leading to substantial heterogeneity. Future analyses including well-designed RCTs are needed before we can draw robust conclusions on the risk of thrombotic events among different dosing schemes of LMWH/F.

Regarding hemorrhagic complications, we demonstrated a lower risk among patients undergoing prophylactic LMWH/F compared to therapeutic doses, as reasonably anticipated. However, there was no association between the risk of any hemorrhagic complications and the administration of no anticoagulation *versus* any LMWH/F, prophylactic *versus* intermediate LMWH/F, and intermediate *versus* therapeutic LMWH/F. Similarly, we found no associations between the LMWH/F dosing (including no administration of anticoagulation) and the risk of ICH. Despite that intermediate doses of LMWH/F seem equally safe with prophylactic LMWH/F regarding hemorrhagic complications, future RCTs are warranted for the assessment of the true impact of different LMWH/F dosing regimens on the hemorrhagic complications and the cost-benefit balance in patients with COVID-19 infection.

Our meta-analysis focuses only on the effects of LMWH/F on all-cause mortality, arterial and venous thromboembolic events and hemorrhagic phenomena in patients with COVID-19. Results from previously published systematic reviews and meta-analyses examining the mortality risk among COVID-19 receiving different doses of anticoagulation are in line with our results, although they have also included other types of antithrombotics. Indeed, Kamel *et al.*[54] in their meta-analysis reported that in-hospital anticoagulation was associated with a beneficial effect on mortality, while Wijaya *et al.*[55] found a tendency toward reduced mortality among mechanically ventilated patients who received therapeutic anticoagulation. Anticoagulation was also associated with lower mortality rate in the systematic review and meta-analysis conducted by Parisi *et al.*[56] However, the aforementioned meta-analyses had analyzed all types of antithrombotic agents, including oral anticoagulants and unfractionated heparin, while we aimed to exclusively evaluate the effectiveness

and safety of LMWH/F. In addition, our meta-analysis included a larger number of studies.

The main strength of the current meta-analysis is the fact that it has been conducted by a multidisciplinary team, using robust methodological pipeline according to an *a priori* established, PRISMA-based protocol. In addition, we utilized a robust and thorough literature search that was performed by three independent reviewers. Compared to previously published meta-analyses, that included studies with any type of antithrombotic agents, our study focuses only on the effects of LMWH/F, which are the most commonly and widely applied anticoagulants in clinical practice, especially among hospitalized patients due to their ease of use (once or twice daily) and minimal monitoring (compared to unfractionated heparin). Finally, as COVID-19 research is a continuously changing landscape, the living nature of this meta-analysis will allow emerging evidence to shape new results on the effects of LMWH and fondaparinux on mortality risk, thrombotic events, and hemorrhagic complications on a regular basis.

Certain limitations of this report need to be acknowledged. First, there is a lack of a standardized definition of the 'intermediate dose' of LMWH/F; although clinicians use this term empirically for doses that are higher than prophylactic and lower than therapeutic, it is important to follow a universal definition provided by international stakeholders and specified further for each agent by the manufacturers themselves. Second, there are insufficient data on the risks and benefits of anticoagulation administration in mild COVID-19 who do not require hospitalization. As the majority of COVID-19 patients remain outpatients, it will be useful to conclude on the role of LMWH/F in this patient population, especially in the context of pleiotropic effects of unfractionated heparin and heparin-derived drugs. Furthermore, our results should be interpreted cautiously due to the moderate quality and the heterogeneity of the included studies. Pooling together data from RCTs and observational studies and recruiting diverse COVID-19 patients of different disease severity who were treated in different settings are acknowledged as potential limitations that led to further analyses exploring for potential differences between subgroups. We expect that with the emergence of data from well-designed large-scale RCTs, these methodological limitations will soon be mitigated.

Conclusion

Our meta-analysis shows that the risk of all-cause mortality may be reduced in patients who receive intermediate doses of LMWH/F compared to prophylactic doses, based on observational data. Although anticoagulation constitutes a common clinical practice among patients with COVID-19 disease globally, especially among those who require hospitalization, robust evidence from ongoing RCTs defining their risks and benefits as well as the appropriate dosing scheme is warranted. We expect that our living systematic review and meta-analysis will shed light on the role and impact of LMWH/F in COVID-19 disease, as new data emerge from well-designed, high-quality trials.

Acknowledgements

None.

Ethics approval and consent to participate

This study did not require an ethical board approval or written informed consent by the patients according to the study design (systematic review and meta-analysis).

Consent for publication

Not applicable.

Author contributions

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Maria Ioanna Stefanou: Data curation; Formal analysis; Investigation; Methodology; Writing – original draft.

Aristeidis Katsanos: Writing – review & editing.

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Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declared no potential conflicts of interest.

Protocol registration

The protocol of this systematic review and meta-analysis has been registered to the International Prospective Register of Ongoing Systematic Reviews PROSPERO (Registration number: CRD42021229771)

Availability of data and materials

The data that support the findings of this study are available from the corresponding author (GT), upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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