



The Effect of Heparin Full-Dose Anticoagulation on Survival of Hospitalized, Non-critically Ill COVID-19 Patients: A Meta-analysis of High Quality Studies

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Abstract

Background International COVID-19 guidelines recommend thromboprophylaxis for non-critically ill inpatients to prevent thrombotic complications. It is still debated whether full-dose thromboprophylaxis reduces all-cause mortality. The main aim of this updated systematic review and meta-analysis is to evaluate the effect of full-dose heparin-based thromboprophylaxis on survival in hospitalized non-critically ill COVID-19 patients.

Methods A systematic review was performed across Pubmed/Medline, EMBASE, Cochrane Central Register of clinical trials, Clinicaltrials.gov, and medRxiv.org from inception to November 2022. We conducted a meta-analysis of randomized clinical trials (RCTs) comparing full-dose heparin-based anticoagulation to prophylactic or intermediate dose anticoagulation or standard treatment in hospitalized non-critically ill COVID-19 patients. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials and Grading of Recommendations Assessment, Development and Evaluation was applied. The primary outcome was all-cause mortality at the longest follow-up available.

Results We identified 6 multicenter RCTs involving 3297 patients from 13 countries across 4 continents. The rate of all-cause mortality was 6.2% (103/1662) in the full-dose group vs 7.7% (126/1635) in the prophylactic or intermediate dose group (Risk Ratio [RR]=0.76; 95% confidence interval [CI]=0.59–0.98; $P=0.037$). The probabilities of any mortality difference and of $NNT \leq 100$ were estimated at 98.2% and 84.5%, respectively. The risk of bias was low for all included RCTs and the strength of the evidence was “moderate.”

Conclusion Our meta-analysis of high-quality multicenter RCTs suggests that full-dose anticoagulation with heparin or low molecular weight heparin reduces all-cause mortality in hospitalized non-critically ill COVID-19 patients.

Study registration: PROSPERO, review no. CRD42022348993.

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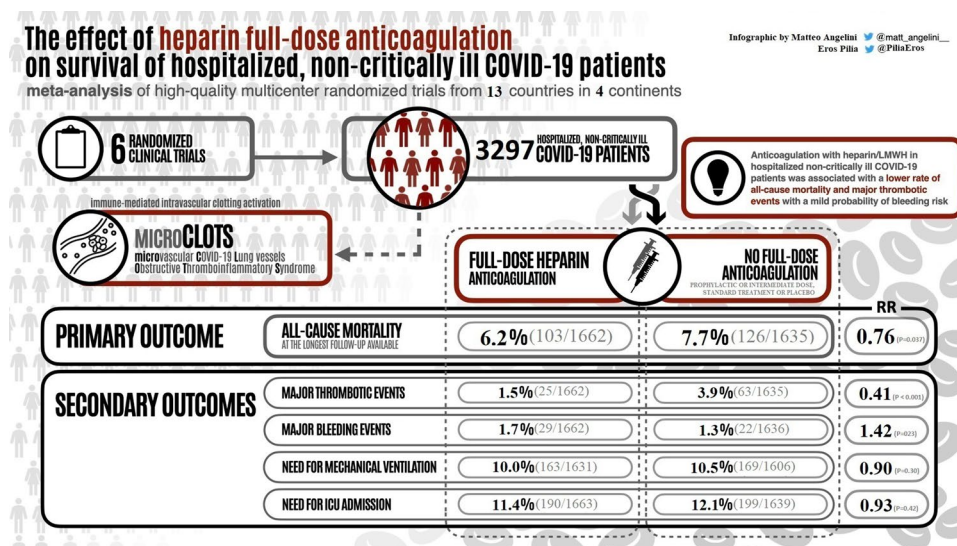
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Graphical Abstract



Keywords Hospital mortality · Heparin · LMWH · Anticoagulant · SARS-CoV-2 · COVID-19

Introduction

Globally, according to the WHO's weekly epidemiological updates until January 9, 2023, there have been 659,108,952 confirmed cases of COVID-19 that caused 6,684,756 deaths [1]. A total of 13,073,712,554 vaccine doses have been administered worldwide so far [1, 2] and most cases of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections are frequently asymptomatic or associated with mild symptoms.

Nowadays, severe COVID-19 cases primarily affect unvaccinated patients or those with comorbidities, and are associated with progressive respiratory failure with a high rate of mortality [3]. In the most severe COVID-19 cases, mortality is related to a particular form of acute respiratory distress syndrome involving vascular inflammation and endothelial injury. The evidence supporting microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS), mediated by an immune-mediated micro-thrombosis, is growing [4]. Thromboprophylaxis has been proposed to prevent MicroCLOTS, although the best timing, method, and dosage of anticoagulation remains to be clarified [5, 6].

International guidelines recommend anticoagulation thromboprophylaxis in hospitalized COVID-19 patients [7–12]. Whereas full-dose anticoagulation reduces major arterial and venous thrombotic events in COVID-19 patients, survival benefits were not documented in non-critically ill patients [13] and in the overall population of COVID-19 hospitalized patients [14].

Consequently, we conducted an updated systematic review and meta-analysis of all available randomized controlled trials (mRCTs) evaluating therapeutic-dose heparin-based anticoagulation in non-critically ill patients and evaluated the impact of thromboprophylaxis on mortality.

Methods

The present systematic review and meta-analysis was conducted following the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] and Cochrane methodology [16]. The original protocol for this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO). The registration number is CRD42022348993.

We designed the review following the PICOS framework: (1) Population: hospitalized non-critically ill COVID-19 patients, (2) Intervention: therapeutic-dose anticoagulation with heparin/LMWH, (3) Comparison: no therapeutic-dose anticoagulation (including standard treatment, placebo, or prophylactic or intermediate dose anticoagulation), (4) Outcome: the primary and secondary outcomes as listed below, (5) Study design: multicenter randomized controlled trials.

Search Strategy and Study Selection

Two reviewers independently searched PubMed/Medline, Embase, the Cochrane Central Register of clinical trials, medRxiv.org and Clinicaltrials.gov (from inception to November 2022) with no language restrictions. Studies were included if there was agreement between the two reviewers, with disagreements resolved by discussion including a third author. The search strategy (Supplementary material) sought to identify RCTs that compared full-dose heparin-based anticoagulation to prophylactic-dose or intermediate-dose heparin-based anticoagulation in hospitalized non-critically ill COVID-19 patients. We included (1) randomized trials (2) enrolling hospitalized non-critically ill adults (age ≥ 18 years) with a positive RT-PCR or antigen test for SARS-CoV-2 viral infection regardless of gender or ethnicity (3) comparing therapeutic-dose anticoagulation with a heparin product (unfractionated or low-molecular weight heparin) versus no therapeutic-dose anticoagulation. We excluded: trials enrolling critically ill patients (defined according to Authors of each individual study); non-hospitalized patients; pediatric patients; and those involving a non-parallel, non-randomized, or quasi-randomized trial design.

Study Outcomes

The primary outcome of our study was all-cause mortality at the longest follow-up available. Secondary outcomes included: the rate of major thrombotic events (as defined by each individual trial); the rate of major bleeding events (as defined by the International Society on Thrombosis and Haemostasis ISTH); the need for mechanical ventilation; and the need for intensive care unit (ICU) admission [17].

Data Abstraction and Risk of Bias Assessment

For each identified trial, two reviewers independently abstracted data about the overall sample size, treatment type and dose, control therapy and the specified outcomes. Trial investigators were contacted by e-mail for additional data if it was not available in the trial manuscript (Supplementary Material Table 1).

Two independent reviewers evaluated the risk of bias with the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2) [18]. The overall risk of bias was classified as “Low,” “Some concerns,” or “High” for each study. Small study effect and publication bias were investigated for primary outcome by visual inspection funnel plot and formally tested using the Egger’s test with STATA v.17 (STATACorp, College Station, USA).

Data Analysis

Analyses were conducted using STATA v.17 (STATACorp, College Station, USA) and RevMan 5.4.1 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Pooled risk ratios (RRs) were calculated for dichotomous outcomes using the fixed-effects Mantel–Haenszel method. The intention-to-treat principle was followed for all analyses.

To contextualize and visualize the findings, we used the RR and 95% CI for each outcome and simulated 100,000 trials on the log scale, generated a representative probability density function on the RR scale using kernel density estimation, and estimated the probability of any benefit ($RR < 1$; bleeding: any harm $RR > 1$) and of a number needed to treat ≤ 100 based on a 1% reduction vs. the overall control event rate on the RR scale (bleeding: number needed to harm based on a 1% increased risk) using STATA v.17 (STATACorp, College Station, USA). Sensitivity analyses were performed by sequentially removing each study and re-assessing the pooled estimates and by changing of summary statistics (RR to odds ratio [OR] or risk difference [RD]).

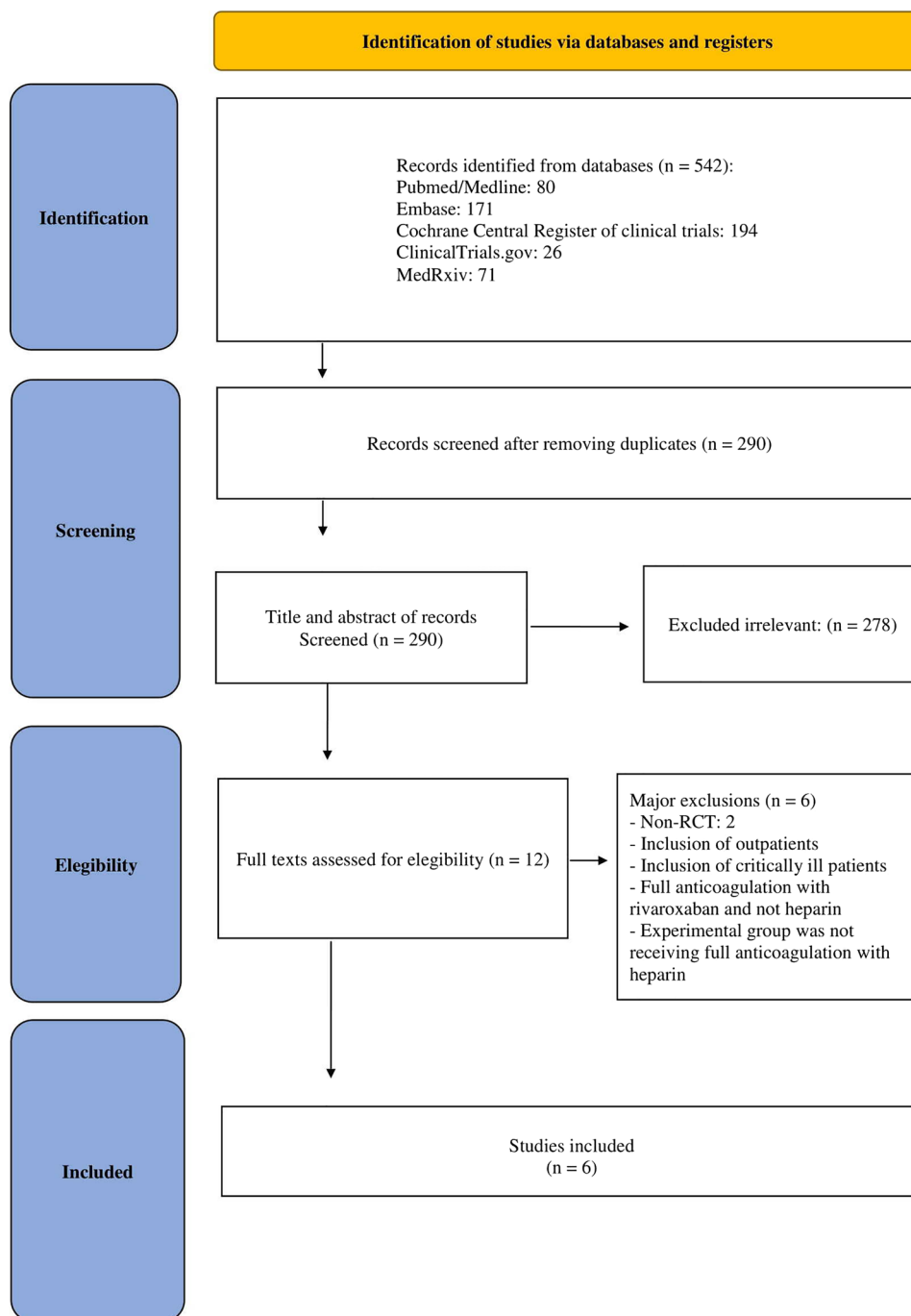
Heterogeneity Analysis

At first, heterogeneity was evaluated by visual inspection of the forest plots, and then formally assessed with the I^2 statistic. We used STATA v.17 (STATACorp, College Station, USA) and RevMan 5.4.1 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to test the heterogeneity hypothesis. We considered statistical heterogeneity for an $I^2 < 25\%$ as low, 26–50% as moderate, and $> 50\%$ as high. Fixed-effects models were used in case of low-to-moderate heterogeneity, while random-effects models were to be used in case of high heterogeneity.

Strength of the Evidence Assessment

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) was applied to rate the strength of evidence. The primary and secondary outcomes were evaluated taking into account the following items: study limitations (risk of bias), inconsistency, indirectness, and imprecision [19]. These items were scored as “not serious concerns,” “serious concerns,” and “very serious concerns.” Publication bias, the number of individuals in each group, and the effect measure of the meta-analysis were also evaluated. At the end, the strength of the evidence was evaluated as very low, low, moderate, or high.

Fig. 1 PRISMA diagram



Results

Study Characteristics

The search strategy in online databases identified potential studies in Pubmed/Medline ($N=80$), Embase ($N=171$), Cochrane Central Register of clinical trials ($N=194$), ClinicalTrials.gov ($N=26$), and MedRxiv ($N=71$). After removing duplicates and applying our eligibility criteria, we identified 6 studies for inclusion in the analysis [20–25] (Fig. 1).

The 6 trials included were multicenter and all included prophylactic or intermediate dose anticoagulation (administered according to local clinical practice guidelines) as control treatment. The studies included a total of 3297 patients (1662 therapeutic-dose heparin-based anticoagulation vs 1635 with prophylactic or intermediate dose anticoagulation) from 13 different countries across 4 continents. (Table 1). The included 6 trials were considered at overall low risk of bias [26] (Fig. 2).

Table 1 Main characteristics of the included studies

mRCT	Full-dose anticoagulation (drug and dosage)	Prophylactic or intermediate dose anticoagulation (drug and dosage)	N patients treatment group	N patients control group	Country	Enrollment period
ATTACC; ACTIV-4a; REMAP-CAP ²⁰	LMWH dosed according to patient weight and CrCl according to local practice; enoxaparin starting at 1 mg/kg twice daily or enoxaparin starting at 1.5 mg/kg once daily; dalteparin: 100 U/kg twice daily or starting at 200 U/kg once daily; tinzaparin 175 anti-Xa units/kg once daily. UFH continuous iv administration per local protocol	LMWH dosed according to patient weight and CrCl according to local practice enoxaparin including (a) 0.5 mg/kg twice daily or (b) 40 mg twice daily; dalteparin 5000 units once daily or 5,000 units twice daily; tinzaparin up to and including (a) 75 anti-Xa units/kg once daily or (b) 4500 units once daily; tinzaparin 4,500 units twice daily; UFH 5,000 units twice or three times daily or 7,500 units three times daily or 10,000 units twice daily	1180	1046	USA, Canada, UK, Brazil, Mexico, Nepal, Australia, the Netherlands, Spain	April 2020–January 2021
PROTHROMCOVID ²¹	Tinzaparin 175 IU/kg/day	Tinzaparin sc 4500 IU/day or 100 IU/kg/day	103	197	Spain	February 2021–September 2021
BEMICOP ²²	Bemiparin 7500 IU qd if bwt between 50 and 70 kg; bemiparin 10,000 IU qd if bwt between 70–100 kg; bemiparin 12,500 IU qd if bwt > 100 kg	Bemiparin 3500 IU sc qd	32	33	Spain	October 2020–May 2021
HEP ²³	Enoxaparin 1 mg/kg sc bid if CrCl \geq 30 mL/min/1.73 m ² ; enoxaparin 0.5 mg/kg sc bid if CrCl 15–29 mL/min/1.73 m ²	UFH up to 22,500 IU sc (divided twice or thrice daily); enoxaparin 30–40 mg sc qd/bid; dalteparin 2500–5000 IU sc qd. If CrCl < 15 mL/min/1.73 m ² , enoxaparin was converted to iv UFH until kidney function improved to CrCl \geq 15 mL/min/1.73 m ²	84	86	USA	May 2020–May 2021

Table 1 (continued)

mRCT	Full-dose anticoagulation (drug and dosage)	Prophylactic or intermediate dose anticoagulation (drug and dosage)	N patients treatment group	N patients control group	Country	Enrollment period
RAPID ²⁴	Enoxaparin 1 mg/kg sc bid or enoxaparin 1.5 mg/kg sc qd or dalteparin 100 IU/kg sc bid or dalteparin 200 IU/kg sc qd or tinzaparin 175 IU/kg sc qd or UFH iv (titrate to institution specific anti-Xa or aPTT values) if CrCl \geq 30 mL/min/1.73 m ² and bmi $<$ 40; enoxaparin 1 mg/kg sc bid or dalteparin 100 IU/kg sc bid or tinzaparin 175 IU/kg sc qd or UFH iv titrate to institution specific anti-Xa or aPTT values if CrCl \geq 30 mL/min/1.73 m ² and bmi \geq 40; UFH iv titrate to institution specific anti-Xa or aPTT values per hospital protocol taking BMI into consideration if CrCl \geq 30 mL/min/1.73 m ²	Enoxaparin 40 mg sc qd or or dalteparin 5000 IU sc qd or tinzaparin 4500 IU sc qd or fondaparinux 2.5 mg sc qd or UFH 5000 UI iv bid/tid if CrCl \geq 30 mL/min/1.73 m ² and bmi $<$ 40; enoxaparin 40 mg sc bid or dalteparin 5000 IU sc bid or tinzaparin 9000 (\pm 1000) UI sc qd or UFH 7500 UI sc tid if CrCl \geq 30 mL/min/1.73 m ² and bmi \geq 40; UFH 5000 UI iv bid/tid if CrCl \geq 30 mL/min/1.73 m ² and bmi $<$ 40 or LMWH per hospital protocol taking BMI into consideration as above; UFH 7500 UI sc tid if CrCl \geq 30 mL/min/1.73 m ² and bmi \geq 40 or LMWH per hospital protocol taking BMI into consideration as above	228	237	USA, Canada, Ireland, Brazil, Saudi Arabia, United Arab Emirates	May 2020–April 2021
SWISS COVID-HEP ²⁵	Enoxaparin 1 mg/kg bid or or therapeutic intravenous or UFH iv if CrCl $<$ 30 mL/min titrate to institution specific anti-Xa values	Enoxaparin once-daily weight-based (20 mg if 40–49.9 kg, 40 mg if 50–99.9 kg, 60 mg if \geq 100 kg), or UFH sc (5000 IU twice daily if $<$ 100 kg, three times daily if \geq 100 kg) if CrCl $<$ 30 mL/min	35	36	Switzerland	April 2020–June 2021

No number, *QD* quaque die, *BID* bis in die, *TID* ter in die, *iv* intravenous, *bwt* body weight, *UFH* unfractionated heparin, *CrCl* creatinine clearance, *BMI* body mass index, *LMWH* low molecular weight heparin, *mRCT* multicenter randomized controlled trial

Fig. 2 Traffic plot of mRCTs included in the meta-analysis

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
ATTACC; ACTIV-4a; REMAP-CAP	+	+	+	+	+	+
PROTHROMCOVID	+	+	+	+	+	+
RAPID	+	+	+	+	+	+
HEP-COVID	+	+	+	+	+	+
BEMICOP	+	+	+	+	+	+
SWISS COVID-HEP	+	+	+	+	+	+

Domains:
 D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 + Low

All-cause mortality at the longest follow-up available

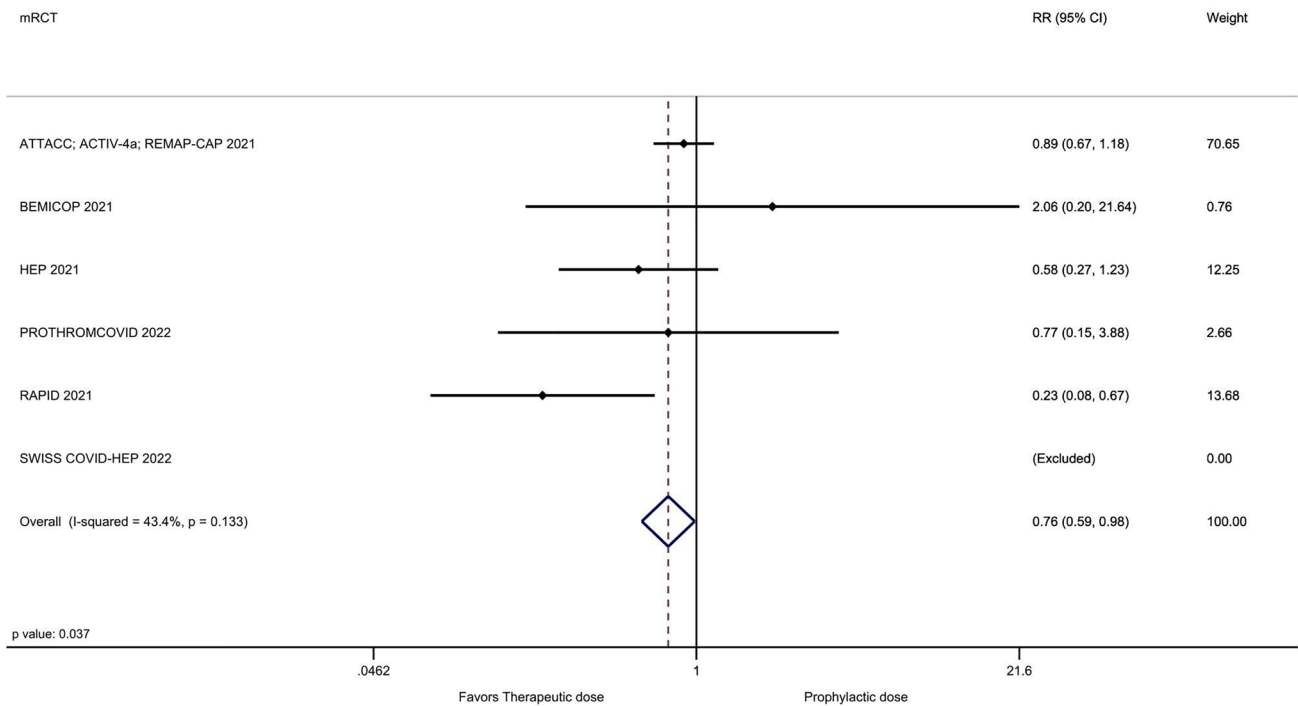


Fig. 3 Forest plot of the rate of all-cause mortality at the longest follow-up available

Quantitative Data Synthesis

Figure 3 shows the forest plot of the rate of all-cause mortality at the longest follow-up available according to the six included randomized studies. All-cause mortality of patients treated with heparin full-dose was 6.2% (103/1662) vs 7.7% (126/1635) in those who received prophylactic or

intermediate dose (risk ratio [RR]=0.76; 95% confidence interval [CI]=0.59–0.98; $P=0.037$; $I^2=43\%$; Egger’s test $P=0.52$). This corresponded to a 98.2% probability of any benefit and to an 84.5% probability that the number needed to treat was ≤ 100 (Supplementary material Fig. 3). Sensitivity analyses showed that the magnitude and direction of the effect size was not modified by sequentially removing

Major arterial and venous thrombotic events

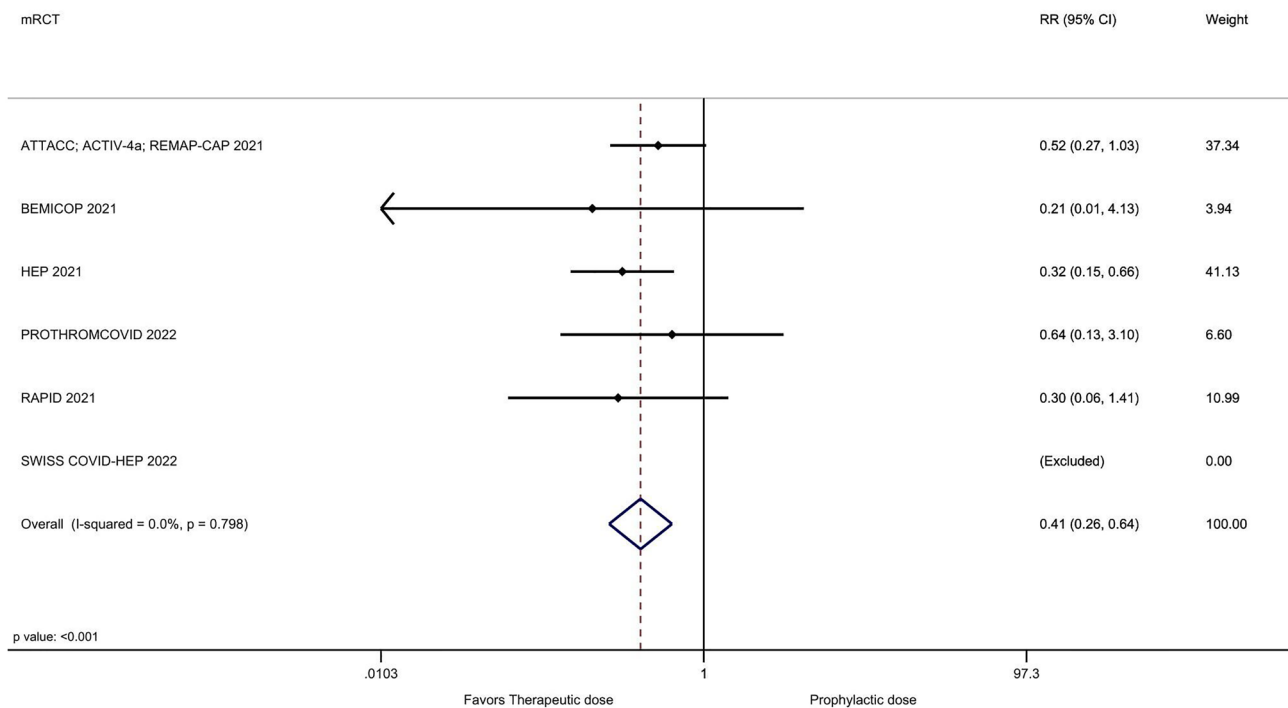


Fig. 4 Forest plot of the rate of major arterial and venous thrombotic events

Major bleeding events

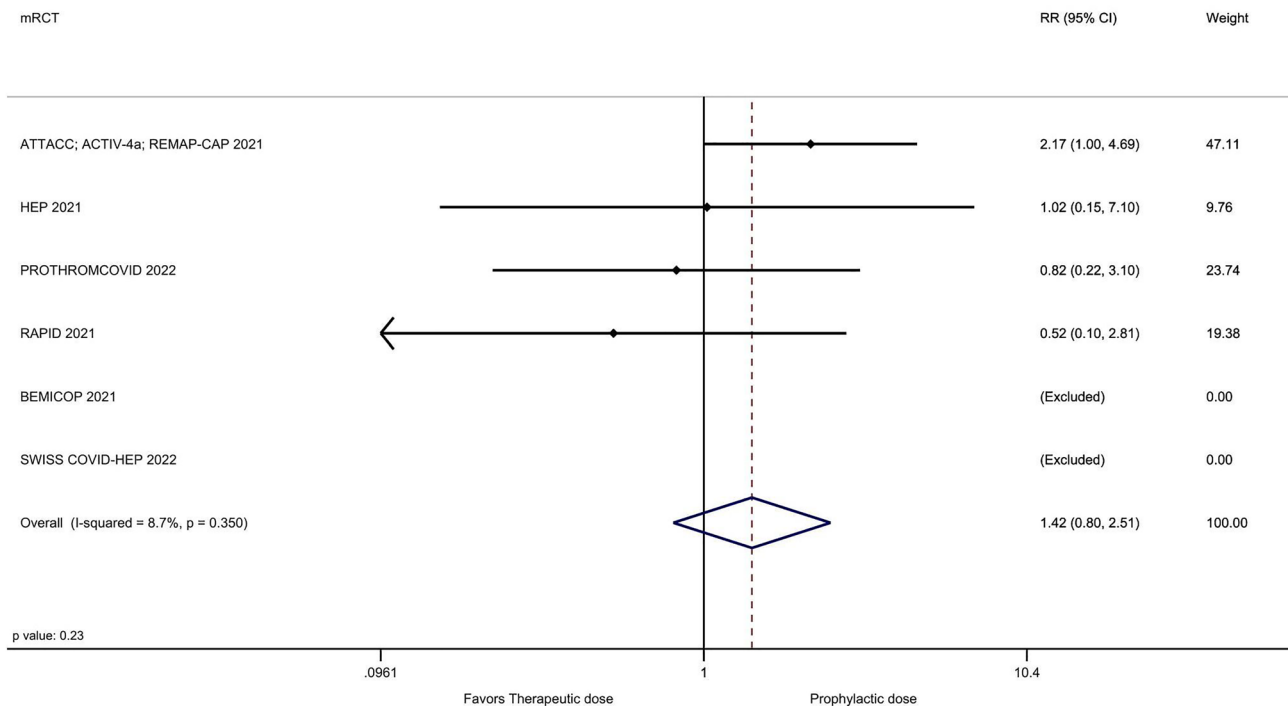


Fig. 5 Forest plot of the rate of major bleeding events

each study and re-assessing the pooled estimates (lowest RR=0.47; 95% CI=0.27–0.81; $P < 0.01$; $I^2 = 22\%$; removing ATTACC; ACTIV-4a; REMAP-CAP and highest RR=0.85; 95% CI=0.65–1.10; $P = 0.22$; $I^2 = 0\%$; removing RAPID). Sensitivity analyses by changing RR to odds ratio (OR = 0.75; CI = 0.57–0.98; $P = 0.04$; $I^2 = 44\%$) or risk difference (RD = -0.02; CI - 0.04, - 0.00; $P = 0.04$; $I^2 = 38\%$) did not result in a change in significance of study findings.

The rate of major arterial and venous thrombotic events was significantly lower for treatment-dose anticoagulation 1.5% (25/1662) vs 3.9% (63/1635) with prophylactic or intermediate dose (RR = 0.41; 95% CI = 0.26–0.64; $P < 0.001$; $I^2 = 0\%$; Fig. 4; Supplementary material Fig. 4). The magnitude and direction of findings did not change with the sequential removal of each trial (lowest RR = 0.29; 95% CI = 0.15–0.57; $P < 0.001$; $I^2 = 0\%$; removing ATTACC; ACTIV-4a; REMAP-CAP and highest RR = 0.47; 95% CI = 0.26–0.83; $P < 0.01$; $I^2 = 0\%$; removing HEP). The rate of major bleeding with treatment-dose anticoagulation was 1.7% (29/1662) vs. 1.3% (22/1636) in those receiving prophylactic or intermediate dose (RR = 1.42; 95% CI = 0.80–2.51; $P = 0.23$; $I^2 = 9\%$; Fig. 5; Supplementary material Fig. 5). This corresponded to an 88.4% probability of increased bleeding with only a 24.4% probability that the number needed to harm would be ≤ 100 . The other secondary outcomes are presented in (Table 2 and Supplementary Material Figs. 1, 2, 6, 7).

Strength of the Evidence Assessment

According to the GRADE approach (Supplementary Material Table 2) there were not “very serious concerns” about

the risk of bias, inconsistency, indirectness, and imprecision [19]. The strength of evidence was moderate for the primary outcome (all-cause mortality), for major bleeding events and for need for mechanical ventilation, while it was high for major arterial and venous thrombotic events and for need for ICU admission.

Discussion

Key Findings

Our systematic review and meta-analysis shows that full-dose thromboprophylaxis (predominantly with LMWH such as enoxaparin, tinzaparin, bemiparin, or dalteparin) might improve survival in hospitalized non-critically ill patients with COVID-19.

Relationship to Previous Studies

There have been a few prior meta-analyses which studied the effect of anticoagulants in hospitalized patients with Covid-19. Important limitations of these previous studies include the following: (1) the combination of direct oral anticoagulants (DOACs) together with heparin-based anticoagulation, (2) the inclusion of patients from different settings (e.g., the inclusion of critically ill patients or outpatients), (3) the inclusion of intermediate doses of anticoagulation in the treatment group, and (4) the inclusion of observational studies which are subject to both have selection and immortal time biases [27–29]. By contrast, our meta-analysis focused

Table 2 Pooled analysis of studies comparing full-dose heparin anticoagulation to prophylactic or intermediate dose anticoagulation

Outcomes	Events/patients full-dose anticoagulation (%)	Events/patients prophylactic or intermediate dose anticoagulation (%)	Risk ratio (95% CI)	P-value	I^2 (%)	Probability RR < 1* (%)	Probability NNT* ≤ 100 *(%)
Primary outcome							
All-cause mortality at the longest follow-up available	103/1662 (6.2%)	126/1635 (7.7%)	0.76 (0.59–0.98)	0.037	43%	98.2	84.5
Secondary outcomes							
Major thrombotic events (arterial and venous)	25/1662 (1.5%)	63/1635 (3.9%)	0.41 (0.26–0.64)	< 0.001	0%	99.9	99.5
Major bleeding events	29/1662 (1.7%)	22/1636 (1.3%)	1.42 (0.80–2.51)	0.23	9%	88.4	24.4
Need for mechanical ventilation	163/1631 (10.0%)	169/1606 (10.5%)	0.90 (0.73–1.10)	0.30	2%	84.4	52.0
Need for ICU admission	190/1663 (11.4%)	199/1639 (12.1%)	0.93 (0.77–1.12)	0.42	0%	77.6	44.4

ICU intensive care unit, CI confidence interval

*RR > 1 and NNH for bleeding

only on full-dose heparin-based thromboprophylaxis involving non-critically ill hospitalized COVID-19 patients.

In 2021, Giossi et al. did not find a difference in overall all-cause mortality between prophylactic-dose and full-dose of anticoagulation. However, they included trials with heterogeneous treatment (e.g., apixaban or heparin) and high risk of bias studies (e.g., observational) in their analysis [30].

In 2022, Jorda A. et al. included patients receiving heterogeneous treatment (i.e., rivaroxaban or heparin) in different settings of care (critically ill and non-critically ill patients or outpatients) [31]. In addition, the intervention group of their meta-analysis included patients who were not subjected only to full-dose thromboprophylaxis due to the inclusion of the INSPIRATION trial and the X-COVID trial [32, 33].

Significance of Study Findings and What this Study Adds to Our Knowledge

SARS-CoV-2 induced infection, compared with other respiratory infections, seems to be associated with higher rates and severity of thrombotic complications which are associated with worse patient outcomes [10]. Consequently, several international guidelines recommend heparin-based thromboprophylaxis in all COVID-19 hospitalized patients [9, 11, 12]. The suitable dosage (full-dose or intermediate or prophylactic dose) of thromboprophylaxis is still debated [5, 12]. However, practical position statements already suggest that in high thrombotic risk, non-critically ill patients, a full-dose thromboprophylaxis is recommended, taking into consideration the individual patient's bleeding risk [34].

Severe forms of COVID-19 seem to be linked to the formation in situ of micro-clots caused by an abnormal activation of the immune system in the lungs [4]. It has been hypothesized that anticoagulant therapy may exert a prophylactic role against these immune-thrombotic events by preventing thrombi formation and progression and, furthermore, that this benefit may best be demonstrated early [7] because anticoagulants may have a lesser ability to act on already formed thrombi [8]. In our updated systematic review and meta-analysis of randomized controlled trials involving non-critically ill hospitalized patients, we demonstrated that thromboprophylaxis with therapeutic-dose heparins (primarily LMWH) was associated with a statistically significant reduction of all-cause mortality and thrombotic events balanced with a modest probability of increased major bleeding. We suggest that the overall benefits outweigh the disadvantages and that for most non-critically ill patients at low risk of bleeding, thromboprophylaxis with LMWH should be recommended. Whether or not patients receiving other forms of thromboprophylaxis at admission should be switched to therapeutic-dose heparin-based thromboprophylaxis is an important question for future research.

The reason of the differences in results of previous meta-analyses grouping critically ill and non-critically ill patients is likely related to this aspect. Final results of our meta-analysis show overall benefits of full-dose anticoagulation in hospitalized non-critically ill COVID-19 patients rather than disadvantages. In addition, because the most favorable thromboprophylactic approach during hospitalization is still not defined, our results may help physicians in the decision-making process when treating non-critically ill COVID-19 patients. Our results can help in reducing COVID-19 all-cause in hospital mortality over time and the consequences of venous thromboembolism (e.g., deep vein thrombosis, pulmonary embolism) and arterial thromboembolism (e.g., myocardial infarction and ischemic stroke) in hospitalized non-critically ill COVID-19 patients [35–38].

Furthermore, there are numerous plausible biological explanations for ancillary beneficial properties of heparin in terms of antiviral effects [39, 40]. Several mechanisms were suggested and are still a research object: (1) the capability of LMWH to bind with high affinity IFN γ , (2) the capability of heparin to influence the biological activity of IL-6 by binding either IL-6 or IL-6/IL-6R α , (3) the heparin capability to inhibit multiple coagulation proteases, some of which might be specific to COVID-19, determining an overall anti-inflammatory action [41]. Indoubitably more clinical evidence is required to clarify heparin antiviral mechanisms of action and its capability to influence infectious conditions such as COVID-19.

Strengths and Limitations of the Study

The main strength of this meta-analysis is the high quality of the low risk of bias multicenter RCTs included [20–25]. Generalizability seems likely as the included patients were not considered critically ill and were recruited from 13 different countries across 4 continents. Disease progression may be too advanced or bleeding complications too high-risk in critically ill patients for them to benefit from full-dose anticoagulation. Another aspect to note is that the use of heparins was heterogeneous across the 6 trials and it is not possible to attribute clinical benefits to a specific molecule. Importantly, few patients were treated with therapeutic dose unfractionated heparin and so the implications for patients with advanced renal dysfunction, for whom LMWH are relative contraindicated, are less clear. Anyway, following Cochrane indications, meta-regression analysis was not included in our investigation because the pooled analysis included fewer than ten studies [42]. To note, meta-analyses should be considered hypothesis-generating, and hence our results remain speculative. Studies included in our analysis included data from the earlier phases of the pandemic when multiple reinfections were uncommon and vaccination was not widely implemented. Our findings may not apply to

current COVID-19 epidemiology. However, coagulopathy in COVID-19 patients is still a field of research and there is a need for more structured clinical trials to make physicians able to take precise decisions regarding thromboprophylaxis in COVID-19 patients [43, 44]. In addition, the role of intermediate dose heparin thromboprophylaxis in non-critically ill patients has not been adequately studied in the available RCTs [34]. We searched also for preprint studies, which may be at high risk of bias [45]. However, all of the identified and included trials were published on peer-reviewed journals.

Conclusion

Pooled data from high-quality multicenter randomized trials suggest a reduction in all-cause mortality at the longest follow-up available in hospitalized non-critically ill COVID-19 patients receiving full-dose heparin-based thromboprophylaxis. This is associated with a significant reduction in thrombotic events with the benefits being partly offset by a modest probability of increased bleeding. Overall, the benefits suggest that therapeutic-dose heparin-based thromboprophylaxis should be recommended in most non-critically ill patients who are not at high risk of bleeding.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00408-023-00599-6>.

Author Contributions EP: conceptualization, visualization, data curation, writing—review & editing, formal analysis, writing—original draft. AB: conceptualization, visualization, data curation, writing—review & editing, writing—original draft. SF: conceptualization, visualization, data curation, writing—original draft. TCL: visualization, formal analysis, writing—review & editing. AZ: conceptualization, project administration, data curation, visualization writing—original draft, writing—review & editing, supervision. GF: conceptualization, resources, writing—original draft, supervision. GL: conceptualization, project administration, data curation, visualization writing—original draft, writing—review & editing, supervision.

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Declarations

Conflict of interest The authors declare they have no conflict of interest.

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