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Efficacy and safety of heparin full-dose anticoagulation in hospitalized non-critically ill COVID-19 patients: a meta-analysis of multicenter randomized controlled trials

Eros Pilia[1,2] · Alessandro Belletti[3] · Stefano Fresilli[3] · Gabriele Finco[1,2] · Giovanni Landoni[3,4]

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Abstract
Arterial and venous thrombotic events in COVID-19 cause significant morbidity and mortality among patients. Although international guidelines agree on the need for anticoagulation, it is unclear whether full-dose heparin anticoagulation confers additional benefits over prophylactic-dose anticoagulation. This systematic review and meta-analysis aimed to investigate the efficacy and safety of heparin full-dose anticoagulation in hospitalized non-critically ill COVID-19 patients. We searched Pubmed/Medline, EMBASE, Clinicaltrials.gov, medRxiv.org and Cochrane Central Register of clinical trials dated up to April 2022. Randomized controlled trials (RCTs) comparing full-dose heparin anticoagulation to prophylactic-dose anticoagulation or standard treatment in hospitalized non-critically ill COVID-19 patients were included in our pooled analysis. The primary endpoint was the rate of major thrombotic events and the co-primary endpoint was the rate of major bleeding events. We identified 4 studies, all of them multicenter, randomizing 2926 patients. Major thrombotic events were 23/1524 (1.5%) in full-dose heparin anticoagulation versus 57/1402 (4.0%) in prophylactic-dose [relative risk (RR) 0.39; 95% confidence interval (CI) 0.25–0.62; p‹0.01; $I^2 = 0\%$]. Clinical relevant bleeding events occurred in 1.7% (26/1524) among patients treated with heparin full anticoagulation dose compared to 1.1% (15/1403) in prophylactic-dose group (RR 1.60; 95% CI 0.85–3.03; p = 0.15; $I^2 = 20\%$). Mortality was 6.6% (101/1524) versus 8.6% (121/1402) (RR 0.63; 95% CI 0.33–1.19; p = 0.15). In this meta-analysis of high quality multicenter randomized trials, full-dose anticoagulation with heparin was associated with lower rate of major thrombotic events without differences in bleeding risk and mortality in hospitalized non critically ill COVID-19 patients.
Study registration PROSPERO, review no. CRD42022301874.

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

Highlights

- Full anticoagulation reduces thrombosis in hospitalized non-critically ill COVID-19 patients
- Full anticoagulation does not increase bleeding in hospitalized non-critically ill COVID-19
- We present findings of meta-analysis of multicenter randomized controlled trials
- Anticoagulation with full-dose heparin/LMWH is overall beneficial to COVID-19 patients
- Randomized evidence supports the use of full-dose heparin/LMWH in COVID-19 patients

✉ Giovanni Landoni
landoni.giovanni@hsr.it

[1] Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy

[2] Department of Anesthesia, Resuscitation and Pain Therapy, University of Cagliari, Cagliari, Italy

[3] Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

[4] School of Medicine, Vita-Salute San Raffaele University, Milan, Italy

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection lead to death over 6 million of people worldwide and it represents a challenge for all healthcare systems [1] .

There is increasing evidence that SARS-CoV-2 infection causes immune-mediated micro-thrombosis due to endothelial injury and vascular inflammation, which has been linked to development of COVID-19 associated acute respiratory distress syndrome (ARDS) and multiple organ failure. In particular, several studies suggested that immunothrombosis has a key role in hypoxemic respiratory failure, the most common presentation of severe COVID-19. The term MicroCLOTS (Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) has been suggested to describe this particular type of ARDS [2] . Therefore, it has been hypothesized that early initiation of anticoagulation may prevent further disease progression. However, the best timing of initiation of anticoagulation remains to be determined. Furthermore, it is unclear whether full-dose therapeutic anticoagulation may confer additional advantage over a prophylactic regimen.

Prior clinical trials [3, 4] and meta-analyses [5, 6] showed contrasting results in terms of clinical benefits of anticoagulation. This heterogeneity in findings is probably related to the inclusion in meta-analyses of non- randomized controlled trials (RCTs), inclusion of patients with highly variable disease severity (from outpatients to patients requiring ICU admission) and lack of data from the most recent trials.

We therefore conducted an updated systematic review and meta-analysis of available RCTs to investigate efficacy and safety of full-dose anticoagulation with heparin in hospitalized, non-critically ill patients with COVID-19.

Methods

This systematic review and meta-analysis was reported according to the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7] and Cochrane methodology [8] . The protocol was registered in PROSPERO (CRD42022301874).

The review question was designed with the PICOS (Population, Intervention, Comparison, Outcome, Study design) framework: Population: hospitalized, non-critically ill COVID-19 patients; Intervention: full-dose anticoagulation with heparin; Comparison: no full-dose anticoagulation (including standard treatment, placebo, or prophylactic-dose anticoagulation); Outcome: any of the primary and secondary outcomes as listed below; Study design: randomized controlled trials.

Search strategy and study selection

Two trained, independent authors searched PubMed/Medline, Embase, medRxiv.org, the Cochrane Central Register of clinical trials and Clinicaltrials.gov (last updated April 2022) for appropriate studies. In addition, references of review articles and included RCTs were screened to identify additional studies. Studies were only included if there was agreement between the two authors and disagreements were resolved by discussion involving a third reviewer. No language restrictions were applied. We designed a search strategy to include RCTs comparing therapeutic-dose of heparin anticoagulation to heparin prophylactic-dose utilization in hospitalized non-critically ill COVID-19 patients. Inclusion criteria were: (1) randomized trials, (2) that enrolled hospitalized, non-critically ill adults (age $\geq$ 18 years with a confirmed diagnosis of respiratory SARS-CoV-2 viral infection (RT-PCR or antigen testing) irrespective of age, gender or ethnicity, (3) comparing full-dose anticoagulation with heparin versus no full-dose anticoagulation. Exclusion criteria were: studies enrolling critically ill patients (defined according to Authors of each individual study), pediatric patients, non-hospitalized patients, a non-parallel design, a non-randomized or quasi-randomized study design. We performed our search strategy on PubMed and Embase in advanced mode with Boolean operators (all search strategies are available in the Supplementary material).

Study outcomes

The primary outcome of our study was the rate of major thrombotic events, defined according to Authors of each individual study. Co-primary outcome was rate of major bleeding events, defined according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH) [9] .

Secondary outcomes were: all-cause mortality at the longest follow-up available; need for mechanical ventilation; a composite of death or need for mechanical ventilation; need for ICU admission; a composite of death or need for ICU admission.

Data abstraction and risk of bias assessment

Two trained authors separately abstracted data on study sample size patients, treatment type and dose, major thrombotic events (arterial and venous), clinical relevant bleeding events, need of ICU admission data (if this was missing we used intubation rate), need of intubation or any mechanical ventilation, and

mortality at the longest follow-up available. We contacted by e-mail authors of the studies to obtain additional from investigators when not available in manuscripts (Supplementary material Table 1).

Risk of bias of included trials was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions and using the recommended version 2 of the Cochrane risk-of- bias tool for randomized trials (RoB 2) [10] . We assessed separately the fours items and we evaluated the potential risk of bias as "Low", "Some concerns" or "High" for each study. RCTs included in the final analysis were assessed as high quality with low risk of bias. Small study effect and publication bias were assessed for primary endpoint by visual inspection funnel plot. Funnel plot asymmetry was assessed with Egger's linear regression method performed using STATA 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

Statistical analysis

All computations related to the outcomes were performed with 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 Mantel–Haenszel statistical method and we presented RR with 95% confidence intervals (CI). For pooled outcome analyses, a *p* value of less than or equal to 0.05 was considered significant.

All analyses followed the intention-to-treat principle whenever possible. For trials which did not report intention-to-treat data we used data as available in the manuscript.

Heterogeneity analysis

Heterogeneity was firstly assessed through visual inspection of the forest plots, and then estimated using the I^2 statistic. Statistical heterogeneity hypothesis was tested using RevMan 5.4.1 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and we considered an I^2 of 25%, 26–50%, and > 50% as low, moderate, and high heterogeneity, respectively. Fixed-effects model was used in case of low statistical heterogeneity, while random-effects model was used in case of moderate-to-high statistical heterogeneity.

Results

Study characteristics

Our database and reference scanning initially yielded a total of 230 articles (Fig. 1). A total of 4 studies randomizing 2926 patients (1524 receiving full-dose heparin anticoagulation and 1402 receiving control treatment) were included in the analysis [11–14] . All studies were multicenter and had prophylactic-dose anticoagulation (administered according to local practice and guidelines, and clinician judgement) as control treatment.

In terms of populations the trials enrolled patients from 12 different countries in 4 continents and all included studies were published in 2021 (Table 1 shows the main characteristics of the included studies). Overall, risk of bias analysis showed that all included trials were at low risk of bias [15] (Fig. 2).

Quantitative data synthesis

Major thrombotic events (arterial and venous) occurred in 1.5% (23/1524) among patients treated with heparin therapeutic-dose compared to 4.0% (57/1402) in those that received prophylactic-dose [relative risk (RR) 0.39; 95% confidence interval (CI) 0.25–0.62; p < 0.01; $I^2 = 0\%$; Egger's test p = 0.47] (Fig. 3).

Sequential removal of each trial did not change magnitude and direction of treatment effect for the primary outcome (lowest RR 0.30; 95% CI 0.16–0.58; p < 0.01; $I^2 = 0\%$; removing ATTACC; ACTIV-4a; REMAP-CAP and highest RR 0.45; 95% (CI 0.25–0.83; p = 0.01; $I^2 = 0\%$; removing HEP).

Clinical relevant bleeding events occurred in 1.7% (26/1524) among patients treated with heparin full anticoagulation dose compared to 1.1% (15/1403) in prophylactic-dose group (RR 1.60; 95% CI 0.85–3.03; p = 0.15; $I^2 = 20\%$) (Fig. 4).

Mortality at the longest follow-up available among patients treated with heparin therapeutic-dose was 6.6% (101/1524) compared to 8.6% (121/1402) in those that received prophylactic-dose (RR 0.63; 95% CI 0.33–1.19; p = 0.15; $I^2 = 58\%$) (Fig. 5).

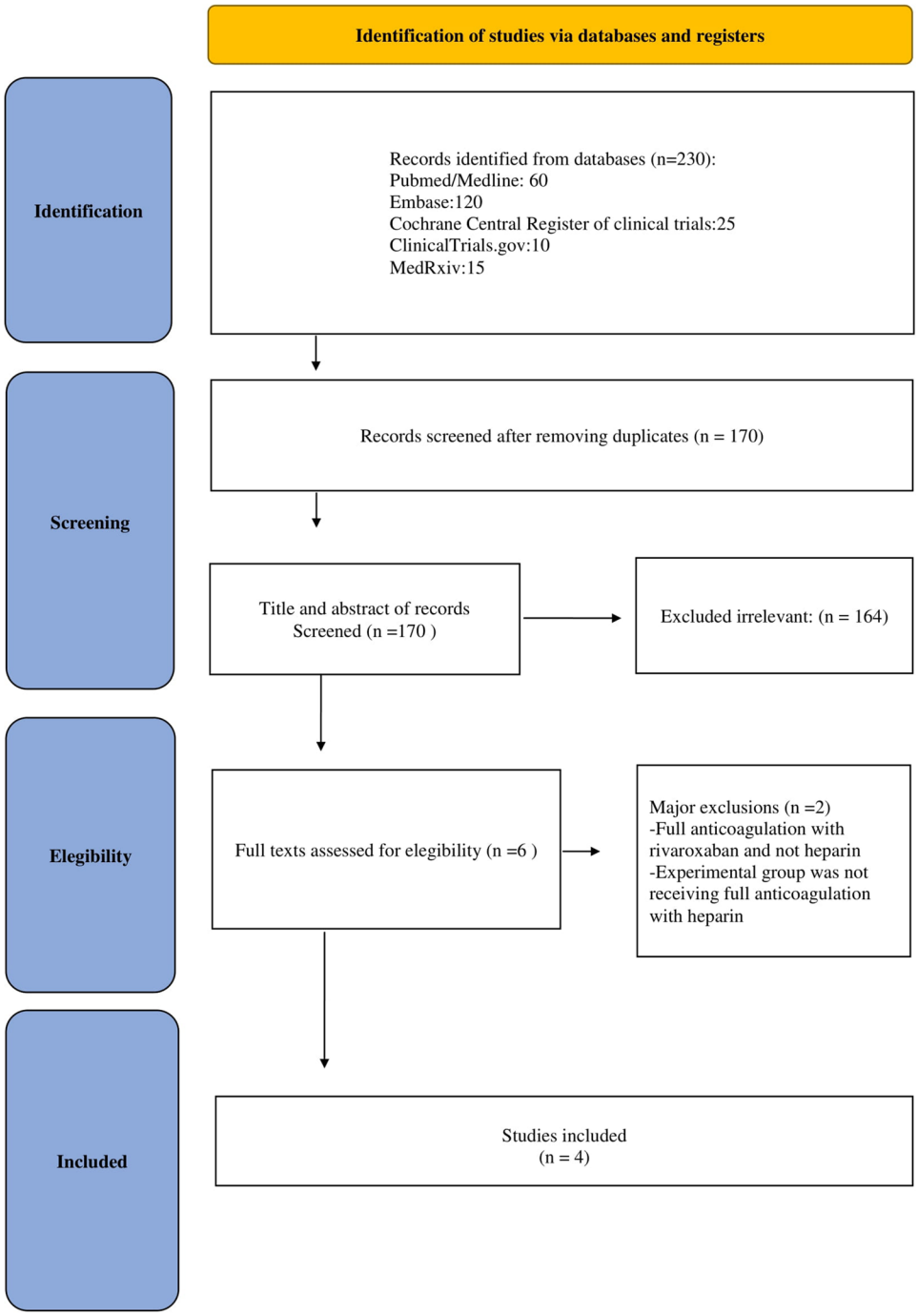
All secondary endpoints showed a trend in favour of full-dose anticoagulation as reported in Table 2 and Supplementary material Figs. 1–5.

Discussion

Key findings

The main finding of our systematic review and meta-analysis is that heparin full-dose anticoagulation treatment (either enoxaparin, bemiparin, other LMWH, or UFH) significantly reduced major thrombotic events in hospitalized non critically ill COVID-19 patients, with no differences in the risk of bleeding events and mortality.

Fig. 1 PRISMA flow chart



Relationship to previous studies

Few meta-analyses summarized this topic but they included heterogeneous treatment (e.g., RCT on rivaroxaban rather than heparin) and settings (e.g., mixing critically and non-critically ill studies) [16] . In 2021 Reis et al. reported that therapeutic-dose anticoagulation may decrease a composite of any thrombotic event or death with a risk of major bleeding [5] . Similarly, Wills et al. found that full-dose anticoagulation compared to prophylaxis decreased the risk of venous thromboembolism events but increased major bleeding events risk [17] . In another meta-analysis, Sholzberg M. et al.; 2021 found a reduction in the composite outcome of death or invasive mechanical ventilation [odds ratio (OR) 0.77; 95% CI 0.60–0.98], and death or any thrombotic event in moderately ill patients (OR 0.58; 95% CI 0.45–0.77) with a nonsignificant increase in major bleeding. We added to their analysis since we identified and included a further RCT [6] . Compared to previous studies, noteworthy aspects of our meta-analysis are the decisions to focus our attention

Table 1 Main characteristics of the included studies

Study	No patients treatment group	No patients control group	Therapeutic-dose anticoagulation (drug and dosage)	Prophylactic-dose anticoagulation (drug and dosage)	Country	Study design and enrollment period
ATTACC; ACTIV-4a; REMAP-CAP [11]	1180	1046	**LMWH** dosed according to patient weight and creatinine clearance according to local practice and policy: **enoxaparin** starting at 1 mg/kg twice daily or **enoxaparin** starting at 1.5 mg/kg once daily; **dateparin:** 100 U/kg twice daily or starting at 200 U/kg once daily; **tinzaparin** 175 anti-Xa units/kg once daily. **UFH** continuous intravenous administration per local protocol	**LMWH** dosed according to patient weight and creatinine clearance according to local practice and policy: **enoxaparin** 40 mg once daily, up to and including (a) 0.5 mg/kg twice daily or (b) 40 mg twice daily; **dalteparin** 5000 units once daily *or* 5000 units twice daily; **tinzaparin** up to and including (a) 75 anti-Xa units/kg once daily or (b) 4500 units once daily; **tinzaparin**: 4500 units twice daily. **UFH** 5000 units twice or three times daily or 7500 units three times daily or 10,000 units twice daily	USA, Canada, UK, Brazil, Mexico, Nepal, Australia, the Netherlands, Spain	mRCT (April 21, 2020 to January 22, 2021)
BEMICOP [12]	32	33	**bemiparin** 7500 IU qd if bwt between 50 and 70 kg; **bemiparin** 10,000 IU qd if bwt between 70 and 100 kg; **bemiparin** 12,500 IU qd if bwt > 100 kg	**bemiparin** 3500 IU sc qd	Spain	mRCT (October 2020 to May 2021)
HEP [13]	84	86	**enoxaparin** 1 mg/kg sc bid if CrCl ≥ 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; **enoxaparin** 30–40 mg sc qd/bid; **dalteparin** 2500–5000 IU sc qd. **UFH** treatment dose iv if CrCl ≤ 15 mL/min/1.73 m^2	USA	mRCT (May 8, 2020 to May 14, 2021)

Table 1 (continued)

Study	No patients treatment group	No patients control group	Therapeutic-dose anticoagulation (drug and dosage)	Prophylactic-dose anticoagulation (drug and dosage)	Country	Study design and enrollment period
RAPID [14]	228	237	**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 ≥ 30 mL/min/1.73 m^2 and bmi ˂ 40; **enoxaparin** 1 mg/kg sc bid or **dalteparin** 100 IU/kg sc bid **tinzaparin** 175 IU/kg sc qd or **UFH** iv titrate to institution specific anti-Xa or aPTT values* if CrCl ≥ 30 mL/min/1.73 m^2 and bmi ≥ 40. **UFH** iv titrate to institution specific anti-Xa or aPTT values* or **LMWH** per hospital protocol taking BMI into consideration if CrCl ˂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 ≥ 30 mL/min/1.73 m^2 and bmi ˂ 40; **enoxaparin** 40 mg sc bid or **dalteparin** 5000 IU sc bid or **tinzaparin** 9000 (± 1000) UI sc qd or **UFH** 7500 UI sc tid if CrCl ≥ 30 mL/min/1.73 m^2 and bmi ≥ 40; **UFH** 5000 UI iv bid/tid if CrCl ˂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 tid if CrCl ˂30 mL/min/1.73 m^2 and bmi ˃40 or **LMWH** per hospital protocol taking BMI into consideration as above	USA, Canada,Ireland, Brazil, Saudi Arabia, United Arab Emirates	mRCT (May 29, 2020 to April 12, 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

*Initial bolus dose determined by sites, encouraging use of dosing algorithm designed for treatment of venous thromboembolism. UFH anti-Xa titration was preferred over aPTT if available as achieving a therapeutic aPTT may be challenging in patients with a pro-inflammatory state such as COVID-19

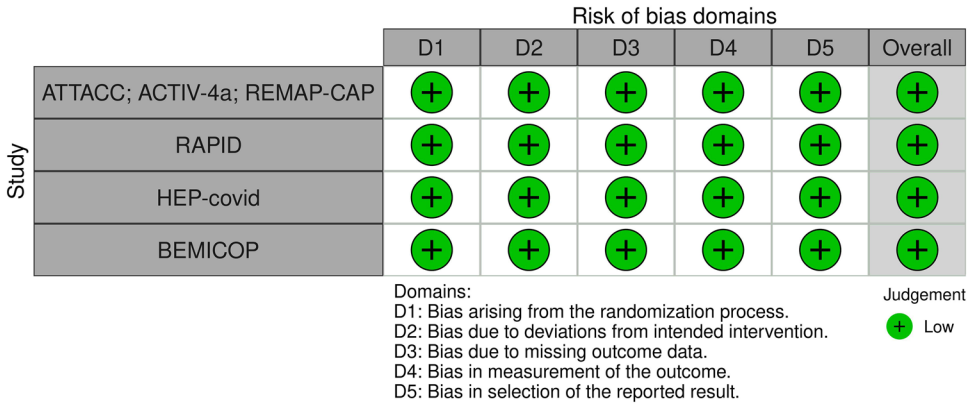


Fig. 2 Traffic plot of RCTs included in the meta-analysis

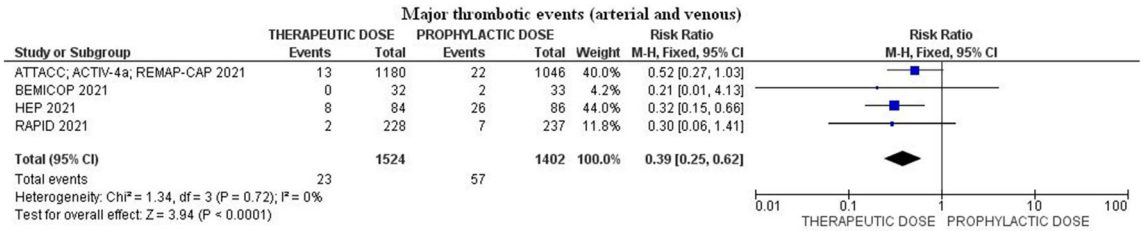


Fig. 3 Forest plot of the rate of major arterial and venous thrombotic events

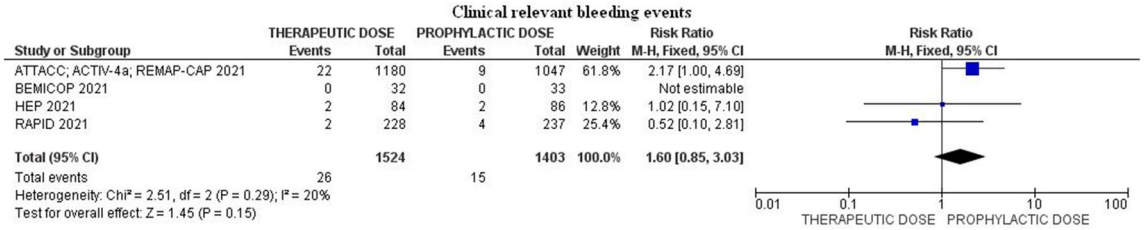


Fig. 4 Forest plot of the rate of clinical relevant bleeding events

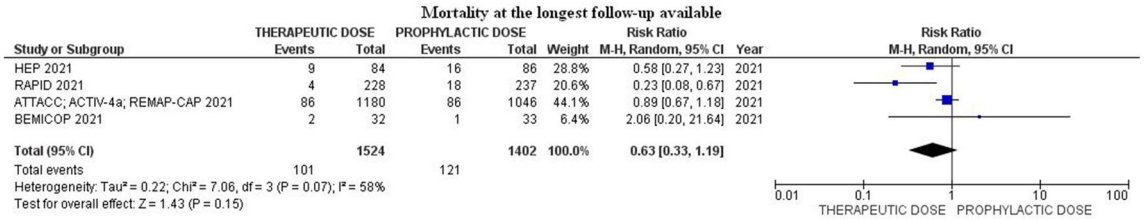


Fig. 5 Forest plot of the rate of mortality at the longest follow-up available

only on full-dose anticoagulation with heparin and to evaluate only non-critically ill patients.

Notably, full-dose anticoagulation in critically-ill patients seems to increase bleeding without being able to improve clinically relevant outcomes. Our meta-analysis can help to improve the management of hospitalized non-critically ill COVID-19 patients since it suggests that the minimal non significant increase in bleeding is couterbalanced by an important reduction in thrombotic events with a trend towards a mortality reduction and an improvement in all clinically relevant outcomes.

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

Outcomes	Events/Total number heparin full anticoagulation (%)	Events/Total number prophylattic anticoagulation (%)	Relative risk (95% CI)	p-value	I^2(%)	Number of included trials
Primary outcomes						
Major thrombotic events (arterial and venous)	23/1524 (1.5%)	57/1402 (4.0%)	0.39 (0.25–0.62)	< 0.01	0	4
Clinical relevant bleeding events	26/1524 (1.7%)	15/1403 (1.1%)	1.60 (0.85–3.03)	0.15	20	4
Secondary outcomes						
Mortality at the longest follow-up available	101/ 1524 (6.6%)	121/1402 (8.6%)	0.63 (0.33–1.19)	0.15	58	4
Need for mechanical ventilation	157/1493 (10.5%)	166/1373 (12.1%)	0.87 (0.71–1.07)	0.18	0	3
Composite outcome death or mechanical ventilation	210/1409 (14.9%)	224/1287 (17.4%)	0.81 (0.59–1.10)	0.18	43	2
Need for ICU admission	173/1525 (11.3%)	182/1406 (12.9%)	0.88 (0.73–1.07)	0.21	0	4
Composite outcome death or ICU admission	165/1409 (11.7%)	177/1287 (13.7%)	0.86 (0.71–1.05)	0.14	0	2

ICU intensive care unit, *CI* confidence interval

Our study aims to investigate full-dose anticoagulation with heparin (either enoxaparin, bemiparin, other LMWH, or UFH). There are plausible biological explanations for anti-viral ancillary beneficial properties of heparin and we considered this when planning our systematic review and meta-analysis.

Significance of study findings and what this study adds to our knowledge

Among hospitalized adults with COVID-19 venous thromboembolism (VTE) such as deep vein thrombosis, pulmonary embolism and arterial thromboembolism (ATE) such as myocardial infarction and ischemic stroke are common and affects morbidity and mortality [18–21] . Furthermore, patients with SARS-CoV-2 infection are likely subjected to the formation of immune mediated pulmonary micro-clots caused by endothelial injury and vascular inflammation [2] . We decided to focus our attention on non-critically ill patients in the hypothesis that full-dose anticoagulation is likely capable of being an effective prophylaxis against immunothrombotic events and in preventing their progression [22] . If COVID-19 MicroCLOTS are similar to the immune-thrombosis model, they are probably resistant to anticoagulants drugs thus heparin may stop the progression of the coagulation cascade avoiding the increase in thrombi size, but is not able to dissolve clots [23] . This aspect may be an explanation of conflicting results of other previous studies that grouped critical and non-critical patients without distinction. In critically ill patients heparin may not be capable of acting on the advanced state of immunothrombi formation characteristic of MicroCLOTS. This particular thrombosis of microcirculation is likely responsive to anticoagulantion only at an early stage of the disease and the correct timing of anticoagulative regimen may be important to prevent the evolution of lung damage.

Several international guidelines recommend heparin-based anticoagulation therapy in all COVID-19 hospitalized patients [24–29] . Despite all these recommendations, the proper dosage of anticoagulant therapy (prophylactic-dose vs full-dose) and the exact time to start anticoagulants remain research objects [30, 31] . The overall results of our meta-analysis show a trend in favour of benefits of full-dose anticoagulation in hospitalized non-critically ill COVID-19 patients. It is imperative to note that all clinical benefits of heparin full-dose anticoagulation regarding clinical worsening must be weighted after a careful evaluation of the bleeding risk for each patient and case-by-case considerations are necessary to better balance the thrombotic risk with that of bleeding.

Our results confirm that, within the context of mild-to-moderate illness, hospitalized, non-critically ill COVID-19 patients benefit from heparin full-dose anticoagulation as prevention for major thrombotic events (arterial and venous). On the other hand heparin full-dose anticoagulation may theoretically increase bleeding risk but the effect size is small and the overall effect on survival seems to be beneficial according to our meta-analysis.

In addition to antithrombotic benefits heparin shows anti-inflammatory, and potentially antiviral effects [32, 33] . The molecular mechanisms of these pleiotropic effects are not fully understood. It is reported in scientific literature that LMWH binds with high affinity to IFNγ fully inhibiting the interaction with its cellular receptor. Furthermore, it

influences the biological activity of IL-6 by binding either IL-6 or IL-6/IL-6Rα. These molecular interactions are likely the basis of the anti-inflammatory action of LMWH and better clarify its ability to favourably influence conditions such as COVID-19 characterized by overexpression of these chemical mediators [34] . More clinical evidence is without doubt required to better clarify these aspects related to heparin full-dose anticoagulation usage in hospitalized non critically ill COVID-19 patients.

Strengths and limitations of the study

The main originality of our study is represented by the high quality and design of the RCTs that we included in the meta-analysis: they were all at low risk of bias. The choice to include only randomized trials allowed us to minimize differences between groups and potential confounders to achieve more transparency and reproducibility. The inclusion of RCTs from different countries and different healthcare realities during a pandemic emergency increases the external validity of the findings. Furthermore, statistical heterogeneity was low in most of the analyses. We are aware that meta-analyses should be considered hypothesis-generating rather than confirmative. Therefore, more adequately powered multicenter RCTs are required before definitive answers on full-dose heparin anticoagulation efficacy and safety can be provided.

Conclusions

Evidence from high-quality randomized trials suggests a significative reduction of major thrombotic events in COVID-19 non-critically ill patients receveing full-dose heparin anticoagulation when compared to propylactic-dose anticoagulation with only a trend towards an improvement in survival.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11239-022-02681-x.

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Declarations

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

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