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Efficacy and safety of two heparin regimens for prevention of venous thromboembolism in hospitalized patients with COVID-19: a meta-analysis

Maria Cristina Vedovati[1] · Mara Graziani[1] · Giancarlo Agnelli[1] · Cecilia Becattini[1]

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Abstract
Venous thromboembolism (VTE) is common in patients with coronavirus disease-2019 (COVID-19). The optimal heparin regimen remains unknown and should balance thromboembolic and bleeding risks. The aim of this study was to evaluate the efficacy and safety of standard or higher heparin regimens for the prevention of VTE in patients hospitalized due to COVID-19. We performed a systematic literature search; studies reporting on hospitalized patients with COVID-19 who received standard heparin prophylaxis vs. high (intermediate or therapeutic) heparin regimens were included if outcome events were reported by treatment group and more than 10 patients were included. Primary study outcome was in-hospital VTE. Secondary study outcomes were major bleeding (MB), all-cause death, fatal bleeding and fatal pulmonary embolism. Overall, 33 studies (11,387 patients) were included. Venous thromboembolic events occurred in 5.2% and in 8.2% of patients who received heparin prophylaxis with at high-dose or standard-dose, respectively (RR 0.71, 95% CI 0.55–0.90, I2 48.8%). MB was significantly higher in patients who received high- compared to the standard-dose (4.2% vs 2.2%, RR 1.94, 95% CI 1.47–2.56, I2 18.1%). Sub-analyses showed a slight benefit associated with high-dose heparin in patients admitted to non-intensive care unit (ICU) but not in those to ICU. No significant differences were observed for mortality outcomes. Heparin prophylaxis at high-dose reduces the risk of VTE, but increased the risk of MB compared to the standard-dose. No clinical benefit for heparin high-dose was observed for ICU setting, but its role in the non-ICU deserves further evaluation. PROSPERO registration number: CRD42021252550.

Keywords Anticoagulants · COVID-19 · Embolism and thrombosis · Major bleeding · Meta-analysis

Introduction

Patients affected by SARS-CoV-2 infection have a wide range of clinical presentations from being asymptomatic to suffer from an acute respiratory distress syndrome which is associated with a high mortality rate [1]. In these patients, the presence of hypoxia, inflammation, platelet activation, endothelial dysfunction, and stasis may predispose to venous thromboembolic events (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) [2]. Indeed, since early, a high incidence of venous thromboembolism (VTE) was observed in hospitalized patients with coronavirus disease 19 (COVID-19) [3]. These complications are considered as predictors of poor prognosis and may contribute to morbidity and mortality [4].

Clinical guidance on the prevention of VTE in COVID-19 patients were promptly published but, as based on relatively low evidences, the recommended strategies were not univocal [2, 5–9]. The use of heparin (unfractionated [UFH] or low molecular weight [LMWH]) at prophylactic doses was recommended by some guidelines and the use of intermediate (any dosage between the standard and the therapeutic one) or therapeutic (full anticoagulation) doses in others.

Noteworthy, patients with COVID-19 might be at risk of excess bleeding due to the imbalances in platelet production and destruction, coagulation factor consumption in the setting of severe inflammation, and use of antiplatelet or anticoagulant agents [2].

✉ Mara Graziani
maragraziani11@gmail.com

Maria Cristina Vedovati
mariacristina.vedovati@unipg.it

[1] Internal, Vascular and Emergency Medicine–Stroke Unit, University of Perugia, Via G. Dottori, Perugia, Italy

Recently published studies comparing prophylactic, intermediate or therapeutic heparin regimens in patients hospitalized for COVID-19 in different clinical settings reported inconsistent reduction of adverse outcomes; thus, the use of higher than prophylactic heparin regimens remains controversial [10–13]. Indeed, these studies were mainly focused on reduction in mortality or on composite outcomes (eg. venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality).

We performed a meta-analysis of published studies on the efficacy (prevention of VTE) and safety of standard or higher heparin regimens for thromboembolic prophylaxis in hospitalized patients with COVID-19.

Methods

A protocol for this study was developed detailing the specific objectives, criteria for study selection, approach to assess study quality, outcomes, and statistical methods (PROSPERO registration number CRD42021252550).

Data sources and searches

We performed an unrestricted search in PubMed, ClinicalTrial.gov, BioRxiv and MedRxiv, from inception through June 13th, 2022. No language restriction was applied. Reference lists of retrieved articles and review articles were manually searched for other relevant studies. The search strategy is reported in the Supplementary material.

Study selection

Two reviewers (M.C.V. and M.G.) performed study selection independently, with disagreements solved through discussion and the opinion of a third reviewer (C.B.). Studies on patients with COVID-19 were considered potentially eligible for the meta-analysis if they met the following predetermined criteria: (a) were randomized clinical trials (RCTs) or observational cohorts (prospective or retrospective); (b) included and reported data on outcome events in patients hospitalized due to SARS-CoV2 infection; (c) included both groups of patients receiving heparin at standard prophylactic dose and at high-dose (intermediate or therapeutic doses); d) reported VTE or bleeding events by groups.

Studies were included in the meta-analysis if the following data were available: (i) number of patients hospitalized due to confirmed COVID-19 who received standard-dose vs. high-dose (intermediate or therapeutic) heparin prophylaxis; (ii) outcome events separately reported by treatment group.

Studies were not eligible for the analysis if: (a) reported on the use of thromboprophylaxis agents other than heparin; (b) included fewer than 10 patients.

The primary study outcome was in-hospital VTE. Secondary study outcomes were in-hospital major bleeding, all-cause-death, fatal pulmonary embolism (PE) and fatal bleeding.

Study outcomes events were reported according to the definition used in the individual studies (e-Table 1).

For duplicate publications, the most complete was considered.

Data extraction and quality assessment

Data were extracted and presented according to the Providing Innovative Service Models and Assessment (PRISMA) criteria [14].

For each study, the following data were extracted: general data (study design, year of publication), population characteristics (mean age, gender), setting (intensive care unit [ICU], non-ICU) and thromboprophylaxis regimen (standard dose, intermediate or therapeutic dose). Information on the following outcomes was collected: VTE, major bleeding and death (all-cause, fatal PE, fatal bleeding).

Study quality was assessed by two reviewers (M.C.V. and M.G.) using Cochrane Collaboration's tool to assess risk of bias in randomized trials, which cover the following bias domains: selection bias, performance bias, detection bias, attrition bias and reporting bias [15]. High quality was defined when at least 6 out of 7 criteria were satisfied (e-Table 2). Similarly, two investigators evaluated the risk of bias in observational studies using the Newcastle–Ottawa quality assessment scale for cohort studies [16]. This scale assesses the representativeness of the sample, ascertainment of the exposure, control of confounding variables, assessment of outcome and adequacy of follow-up, which provides a score ranging from 0 (lowest grade) to 9 (highest grade). High-quality studies were considered when at least 8 out of 9 criteria were satisfied. We resolved disagreements in study data extraction and quality assessment by consensus or by discussion with a third reviewer (C.B.).

Statistical analysis

Study outcomes in patients who received the high-dose (intermediate or therapeutic) were compared with patients receiving standard-dose heparin prophylaxis using a random effect model. To evaluate statistical heterogeneity, we calculated the I^2-index: a value of 25% was defined as low heterogeneity, 50% as moderate heterogeneity, and 75% as high heterogeneity [17]. In case of heterogeneity, subgroup analyses (according to study design, hospital setting, dose of prophylaxis, study quality) and metaregression analyses were performed (according to study design, study quality, hospital setting, dose of prophylaxis).

We expressed comparison between treatment groups by risk ratios (RR) with 95% confidence intervals (CIs) and forest plots. Cells including zero were replaced with 0.5. Main results were also reported as number needed to treat (NNT), number needed to harm (NNH) and likelihood of being helped or harmed (LHH calculated as NNH/NNT) [18].

Subgroup analyses according to study design (RCTs, cohort studies) and hospital setting (ICU or non-ICU) were performed. Separate analyses comparing studies reporting on intermediate-dose vs. standard-dose and comparing therapeutic-dose vs. standard-dose heparin prophylaxis were also performed. In addition, analyses limited to high-quality studies by quality assessment and by study design (retrospective studies excluded) were performed.

Publication bias was assessed by using Egger's regression test and considered significant if p-value was < 0.10.

To assess agreement between reviewers for study selection, we used the kappa statistic, which measures agreement beyond chance.

Analysis was performed with StatsDirect 3.2.10 (StatsDirect Ltd, Wirral, UK).

Results

Overall, 3598 studies were found and 124 were selected as potentially relevant. At the end of the selection process, 33 studies (11,387 patients) satisfied criteria for inclusion in the meta-analysis (Table 1) [10–13, 19–47]. Flow diagram for study selection is reported in e-Fig. 1. Inter-observer agreement for study selection was good (k = 0.82). Ten studies were RCTs, 4 were prospective and 19 were retrospective cohort studies. Sites of MBs are reported in e-Table 1.

Venous thromboembolism

Twenty-three studies (8428 patients) reported on in-hospital VTE: a significant reduction of VTE events was observed in patients receiving heparin high-dose compared to those receiving standard-dose prophylaxis (RR 0.71, 95% CI 0.55–0.90, I2 48.8%) (Fig. 1A). Main results are reported in Table 2. Moderate heterogeneity was observed, metaregression analysis showed not significant influence of study design ($p = 0.092$), study quality ($p = 0.212$), hospital setting ($p = 0.131$), while it seemed associated to dose of heparin prophylaxis ($p = 0.025$). The separate analyses of the different doses of heparin prophylaxis showed persistent heterogeneity (I2 51.5%) for studies reporting on high-dose heparin prophylaxis (not sortable), while for studies reporting on the intermediate and for the therapeutic doses it was low (I2 1.4% and 0.0%, respectively).

Heterogeneity was reduced by exclusion of retrospective studies (RR 0.50, 95% CI 0.36 to 0.69, I2 14.8%) and remained unchanged after exclusion of low-quality studies (RR 0.65, 95% CI 0.50–0.85, I2 38.9%).

In the subgroup analyses of studies reporting separately data in patients admitted to the ICU and to the non-ICU settings, results were similar to those observed in the main analysis (RR 0.70, 95% CI 0.52–0.93, I2 52.1% and RR 0.48, 95% CI 0.26–0.87, I2 0.0%) (Fig. 2A, B). Moderate heterogeneity was found in the sub-analysis on ICU setting that persisted after removing retrospective or low-quality studies. A separate analysis of randomized controlled studies was reported in e-Table 3 and e-Fig. 2.

No significant differences were observed when intermediate heparin doses were compared to standard-dose prophylaxis, but a significant reduction in VTE events was observed when the therapeutic doses were used (e-Table 4).

Egger's test did not reveal publication bias. The NNT was 33, 36 and 78 in the overall population, in the ICU and in the non-ICU patients, respectively. In the separate analysis of intermediate or therapeutic doses NNT was 111 and 33, respectively.

Major bleedings

Overall, 28 studies (10,283 patients) reported on major bleeding. Major bleedings were nearly doubled in patients receiving high-dose heparin regimens compared to those receiving standard-dose (RR 1.94, 95% CI 1.47–2.56, I2 18.1%) (Fig. 1B). Low heterogeneity was observed. Metaregression analyses showed no influence of study deign ($p = 0.272$), hospital setting ($p = 0.304$), study quality ($p = 0.994$), dose of heparin prophylaxis ($p = 0.880$) on heterogeneity. A significant increase of major bleedings was confirmed in the subgroup analyses according to study design, in the ICU setting and when the therapeutic dose was used (Table 2, Fig. 2C, 2D, e-Table 3, e-Table 4 and e-Fig. 3) and when retrospective or low-quality studies were excluded.

Egger's test did not reveal publication bias. The NNH was 50, 33 and 125 in the overall population, in the ICU and inthe non-ICU patients, respectively. In the separate analysis of intermediate or therapeutic doses NNH was 40 and 59, respectively. The LHH was 1.5, 0.9, 1.6 in the overall population, in the ICU and in the non-ICU patients, respectively. In the separate analysis of intermediate or therapeutic doses LHH was 0.4 and 1.8, respectively.

Mortality

Overall, 21 among selected studies (7849 patients) reported data on mortality. All-cause death occurred in 17.7% of patients who received high-dose regimens and in 20.3% of patients receiving standard-dose (RR 0.84, 95% CI

Table 1 Baseline characteristics of the studies included in the meta-analysis

Author, Year	Study design	Setting	Patients (*n*)	Male (%)	Age, years (mean or median)	Follow-up, days (mean or median)	VTE events (%)S/A	MB events (%) D	All-cause death (%)	Prophylactic dose (*N*)	Intermediate or therapeutic dose (*N*)	Quality assessment
Al Raizah, 2021	Retrospective cohort	ICU, non-ICU	604	75.5	49	n.a	n.a. S + A	0.8 ISTG	8.1	Enoxaparin 4000 IU/die or 3000 IU/die; UFH 5000 IU/bid or tid (*N* = 502)	Enoxaparin 4000 IU/bid or 3000 IU/bid, or other dose or full dose; UFH other dose or full dose (*N* = 102)	9*
Atallah, 2020	Retrospective cohort	ICU	182	85.0	49	9	11.5	7.1 ISTH	20.9	Enoxaparin 4000 IU/die or 4000 IU/bid or 3000 IU/die or 3000 IU/bid or 6000 IU/bid or UFH 5000 IU/bid or 5000 IU/bid or 7500 IU/bid according to the BMI, creatinine clearance and D-dimer level (*N* = 83)	Enoxaparin 100 IU/kg/ bid or 80/IU/kg/bid according to the BMI, creatinine clearance and D-dimer level (*N* = 99)	8*
Bellmunt-Montoya, 2020	Retrospective cohort	ICU	230	77.0	61	7	26.5 S + A	2.1 ISTH	5.6	Enoxaparin 4000 IU/die or 50 IU/kg/die (*N* = 127)	Enoxaparin 6000 IU/die or 100 IU/kg/die or 100 IU/kg/bid (*N* = 100)	9*
Blondon, 2022	Randomized	ICU-non ICU	160	69.8	62	30	0.62 S	1.9 ISTH	3.77	Medically ill: Enoxaparin 2000 UI or 4000 UI or 6000 UI die according to weight (cut-off 100 kg) or UFH 5000 UI bid in case of renal clearance < 30 ml/min. Critically ill: Enoxaparin 4000 UI bid or 6000 UI bid according to weight or UFH 15.000/20.000 UI daily according to the weight. (*N* = 80)	Enoxaparin 100 UI/kg bid with ant-Xa assay monitoring if extreme body weithg or CrCl < 50 ml/min or UFH in case of renal clearance < 30 ml/min (*N* = 79)	6#

Table 1 (continued)

Author, Year	Study design	Setting	Patients (*n*)	Male (%)	Age, years (mean or median)	Follow-up, days (mean or median)	VTE events (%)S/A	MB events (%) D	All-cause death (%)	Prophylactic dose (*N*)	Intermediate or therapeutic dose (*N*)	Quality assessment
Chang, 2020	Retrospective cohort	ICU, non -ICU	168	n.a	64	30	30.5	n.a	n.a	UFH 5000 IU/tid or Enoxaparin 4000 IU/die or 3000 IU/bid (*N* = 132)	n.a (*N* = 36)	7*
Dalager-Pedersen, 2020	Prospective cohort	ICU, non-ICU	582	57.6	69	30	n.a	2.6 ISTH	n.a	LMWH at standard prophylactic dose (*N* = 230)	LMWH at intermediate or weight-adjusted therapeutic (*N* = 27)	8*
Fraissé, 2020	Retrospective cohort	ICU	92	79.3	61	n.a	33.7 S	20.6	41.3	n.a. (*N* = 43)	n.a. (*N* = 49)	8*
Goligher, 2021	Randomized	ICU	1098	70.3	61	21	5.6 S	3.0 ISTG	36.3	Enoxaparin 4000 IU/die§; Dalteparin 5000 IU/die§; Tinzaparin 4500 IU/die or 75 anti-Xa IU/die§; UFH 5000 IU/bid or tid§ (*N* = 562)	Enoxaparin 4000 IU/bid or 50 IU/kg/bid, 100 IU/kg/die; 100 IU/kg/bid or 150 IU/kg/die§^; Dalteparin 5000 IU/bid; 100 IU/kg/bid; 200 IU/kg/die§^; Tinzaparin 4500 IU/bid; 175 anti-Xa units/kg/die§^; UFH 7500 IU/tid/die; 10,000 IU/bid; target of aPTT 1.5–2.5 times the UL§^ (*N* = 529)	6#
Gonzales-Porras, 2020	Retrospective cohort	ICU	611	67.5	72	7	1.9	3.6 ISTH	25.0	Enoxaparin 4000 IU/die or Bemiparin 3500 IU/die; Enoxaparin 2000 IU/die or bemiparin 2500 IU/die if creatinine clearance < 20 ml/min (*N* = 422)	Enoxaparin 100 IU/kg/die or bemiparin 5000 IU/die; Enoxaparin 50 mg/kg/die or bepimarin 3500 IU/die if creatinine clearance < 30 ml/min (*N* = 189)	9*

Table 1 (continued)

Author, Year	Study design	Setting	Patients (*n*)	Male (%)	Age, years (mean or median)	Follow-up, days (mean or median)	VTE events (%)S/A	MB events (%) D	All-cause death (%)	Prophylactic dose (*N*)	Intermediate or therapeutic dose (*N*)	Quality assessment
Helms, 2020	Prospective cohort	ICU	179	72.7	62	8	13.9	1.7 WHO	17.3	Enoxaparin at standard prophylactic dose or 6000 IU/bid in obese or UFH 200 IU/kg/die if creatinine clearance < 30 ml/min (*N* = 108)	LMWH 100 IU/kg/bid or UFH 500 IU/kg/die if creatinine clearance < 30 ml/min (*N* = 71)	9*
Jenkins, 2021	Retrospective cohort	ICU	121	53.7	62.5	30	13.4 S	43.2 WHO	59.7	Enoxaparin 3000 UI or 4000 UI die or UFH 5000 Ui bid according to the renal function (*N* = 34)	UFH IV with target aPTT or Enoxaparin 1 mg/kg die or bid according to the renal function (creatinine clearance cut-off 30 ml/min) (*N* = 33)	8*
Jimenéz-Soto, 2021	Retrospective cohort	Non-ICU	321	67.0	54	n.a	1.6	1.6 ISTH	6.5	Enoxaparin 4000 IU/die (*N* = 109)	Enoxaparin 4000 IU/bid or 50 IU/kg/bid or enoxaparin 100 IU/kg/bid (*N* = 212)	5*
Jonmarker, 2020	Retrospective cohort	ICU	152	82.2	61	28	14.5 S + A	3.2 WHO	28.2	Tinzaparin 2500–4500 IU/die or dalteparin 2500–5000 IU/die (*N* = 67)	Tinzaparin > 4500 IU/die or dalteparin > 5000 IU/die or tinzaparin ≥ 175 IU/kg/die or dalteparin ≥ 200 IU/kg/die (*N* = 85)	9*
Lavinio, 2021	Retrospective cohort	ICU	709	78.7	66	13	15.0 S + A	5.5 ISTH	47.2	Enoxaparin at standard prophylactic dose (*N* = 435)	Enoxaparin 50–100 IU/kg/bid or UFH antiXa target 0.3–0.5 or aPTTR target 1.5–2.5 (*N* = 274)	8*

Table 1 (continued)

Author, Year	Study design	Setting	Patients (*n*)	Male (%)	Age, years (mean or median)	Follow-up, days (mean or median)	VTE events (%)S/A	MB events (%) D	All-cause death (%)	Prophylactic dose (*N*)	Intermediate or therapeutic dose (*N*)	Quality assessment
Lawler, 2021	Randomized	Non-ICU	2231	59.1	59	21	1.6 S	1.4 ISTH	7.8	Enoxaparin 4000 IU/die§; Dalteparin 5000 IU/die§; Tinzaparin 4500 IU/die or 75 anti-Xa IU/die§; UFH 5000 IU/bid or tid§ (*N* = 1047)	Enoxaparin 4000 IU/bid or 50 IU/kg/bid, 100 IU/kg/die; 100 IU/kg/bid or 150 IU/kg/die§^; Dalteparin 5000 IU/bid; 100 IU/kg/bid; 200 IU/kg/die§^; Tinzaparin 4500 IU/bid; 175 anti-Xa units/kg/die§^; UFH 7500 IU/tid/die; 10,000 IU/bid; target of aPTT 1.5–2.5 times the UL§^ (*N* = 1180)	6#
Lemos, 2020	Randomized	ICU	20	80.0	n.a	28	20.0	0 TIMI	35.0	Enoxaparin 4000 IU/die if < 120 kg or 4000 IU/bid if > 120 kg; UFH 5000 IU/tid if < 120 kg or UFH 7500 IU/tid if > 120 kg (*N* = 10)	Enoxaparin 100 IU/kg/bid or 75 IU/kg/bid or 100 IU/kg/die according to age and creatinine clearance (*N* = 10)	6#
Llitjos, 2020	Retrospective cohort	ICU	26	76.9	68	7	69.2 S + A	n.a	11.5	LMWH at standard prophylactic dose (*N* = 8)	LMWH or UFH adjusted by anti-Xa activity (*N* = 18)	3*
Lodigiani, 2020	Retrospective cohort	ICU, non-ICU	388	68.0	66	10	2.0 S	n.a ISTH	n.a	LMWH at standard prophylactic dose (*N* = 169)	LMWH weight-adjusted at intermediate or therapeutic (*N* = 134)	8*
Marcos-Jubilar, 2021	Randomized	Non-ICU	65	63.1	62	10	n.a	0 ISTH	0	Bemiparin 3500 IU/die (*N* = 33)	Bemiparin 115 IU/kg die (*N* = 32)	4#
Martinelli, 2021	Retrospective cohort	ICU, non ICU	278	65.1	59	21	13.0	1.4 ISTH	26.7	Enoxaparin 4000 IU/die or 6000 UI/die in obese (*N* = 151)	Enoxaparin 100 IU/kg/bid or 70 IU/kg/bid or 100 IU/kg/die (*N* = 127)	9*

Table 1 (continued)

Author, Year	Study design	Setting	Patients (*n*)	Male (%)	Age, years (mean or median)	Follow-up, days (mean or median)	VTE events (%)S/A	MB events (%) D	All-cause death (%)	Prophylactic dose (*N*)	Intermediate or therapeutic dose (*N*)	Quality assessment
Moll, 2021 +	Retrospective cohort	ICU	205	32	58	30	19.1	7.4 ISTH	26.6	Enoxaparin 4000 IU/die or UFH 5000 IU/bid or tid (*N* = 47)	Enoxaparin 4000 IU/bid or 50 IU/kg/bid if extremes of weight or UFH 7500 IU/tid (*N* = 47)	6*
Motta, 2020	Retrospective cohort	ICU, non-ICU	374	58.9	64	28	n.a	0.8	19.2	Enoxaparin 3000 or 4000 IU/die or UFH 5000 IU/tid (*N* = 299)	Enoxaparin 100 IU/kg/bid or 150 IU/kg/die (*N* = 75)	7*
Morici, 2021	Randomized	Non-ICU	183	62.8	59	30	3.27 S + A	3.27 ISTH/BARC	1.1	Enoxaparin 4000 UI die (*N* = 92)	Enoxaparin 4000 UI bid (*N* = 91)	6#
Musoke, 2020	Retrospective cohort	ICU	300	n.a	66	30	n.a	6.3 ISTH	n.a	LMWH 3000–4000 IU/die or heparin 5000 IU/bid or tid (*N* = 178)	LMWH 100 UI/kg/bid (*N* = 122)	7*
Pancani, 2020	Prospective cohort	Non-ICU	66	57.6	74	n.a	n.a S + A	1.5	n.a	Enoxaparin 4000 IU/die or Enoxaparin 6000 IU/die (*N* = 25)	Enoxaparin 100 IU/kg body weight bid (*N* = 7)	8*
Paolisso, 2020	Retrospective cohort	ICU	450	63	67	7	n.a	0.8	17.5	Enoxaparin 4000 IU/die or 6000 IU/die (*N* = 361)	Enoxaparin 4000 IU/bid or 6000 IU/bid (*N* = 89)	9*
Perepu, 2021	Randomized	ICU	176	55.1	64	30	7.3	2.2 ISTH	17.6	Enoxaparin 4000 IU/die; 3000 IU/bid or 4000 IU/bid if BMI ≥ 30 kg/mq (*N* = 86)	Enoxaparin100 IU/kg/bid; 50 IU/kg/bid if BMI ≥ 30 kg/mq (*N* = 87)	5#
Salisbury, 2020	Retrospective cohort	ICU, non-ICU	294	56.1	73	7	5.6 S	1.0 ISTH	33.3	Dalteparin 5000 IU/die (*N* = 239)	Dalteparin 5000 IU/bid or therapeutic anticoagulation (*N* = 55)	9*
Sadeghipour, 2021	Randomized	ICU	562	57.8	62	30	3.4 S	1.2 BARC	42.0	Enoxaparin 4000 IU/die§^ (*N* = 286)	Enoxaparin 100 IU/kg/die§^ (*N* = 276)	6#

Table 1 (continued)

Author, Year	Study design	Setting	Patients (*n*)	Male (%)	Age, years (mean or median)	Follow-up, days (mean or median)	VTE events (%)S/A	MB events (%) D	All-cause death (%)	Prophylactic dose (*N*)	Intermediate or therapeutic dose (*N*)	Quality assessment
Sholzberg, 2021	Randomized	Non-ICU	465	56.8	60	28	1.7	1.3 ISTH	4.7	Enoxaparin 4000 IU/die°; Dalteparin 5000 IU/die°; Tinzaparin 4500 IU/die°; Fondaparinux 2,5 mg/die; UFH 5000 IU/bid ° (*N* = 237)	Enoxaparin 100 IU/kg/bid or 150 IU/kg/die°; Dalteparin 200 IU/kg/die or 100 IU/kg/bid°; Tinzaparin 175 IU/kg/die°; UFH continuous infusion antiXa or aPTT target (*N* = 228)	6#
Spyropoulos, 2021	Randomized	ICU, non-ICU	253	52.9	67	30	19.8 S + A	3.2 ISTH	22.1	UFH up to 22,500 IU bid or tid; enoxaparin 3000 IU or 4000 IU daily or bid ç; dalteparin, 2500 IU or 5000 IU daily (*N* = 124)	Enoxaparin 100 IU/kg/bid if CrCl ≥ 30 mL/min/1.73 m2 or 50 IU/kg/bid if CrCl 15–29 mL/min/1.73 m2 (*N* = 129)	6#
Taccone, 2020	Retrospective cohort	ICU	40	70.0	61	28	32.5	n.a	50.0	Enoxaparin 4000 IU/die (*N* = 22)	Enoxaparin 4000/IU/bid or therapeutic UFH (*N* = 18)	7*
Voicu, 2020	Prospective cohort	ICU	93	68.8	63	28	40.8 S + A	19.3 ISTH	40.8	Enoxaparin 4000 IU/die or UFH 15,000 IU/die (*N* = 50)	Enoxaparin 40 mg/bid or 1 mg/kg/bid or UFH to reach anti-Xa 0.3–0.6 IU/ml (*N* = 43)	8*

APTT activated partial thromboplastin time, *Bid* twice a day, *BMI* body mass index, *ICU* intensive care unit, *IU* international unit, *LMWH* low molecular weight heparin, *MB* major bleeding, *Tid* three times a day, *UFH* unfractioned heparin, *UL* upper limit, *VTE* venous thromboembolism, *S/A* symptomatic/asymptomatic VTE, *D* definition of MB, *n.a.* not available

+ Only data reported in the propensity score-matched analysis were included

*Newcastle–Ottawa quality assessment scale for cohort studies

#Cochrane risk of bias tool for randomized clinical trials

§Increased dose if creatinine clearance ≥ 30 ml/min and increased body weight or BMI; reduced dose if creatinine clearance < 30 ml/min

^UFH if creatinine clearance ≤ 15 ml/min

°Increased dose if BMI ≥ 40 kg/mq; UFH if creatinine clearance ≤ 30 ml/min

çWeight-based enoxaparin 0.5 mg/kg bid was permitted but strongly discouraged

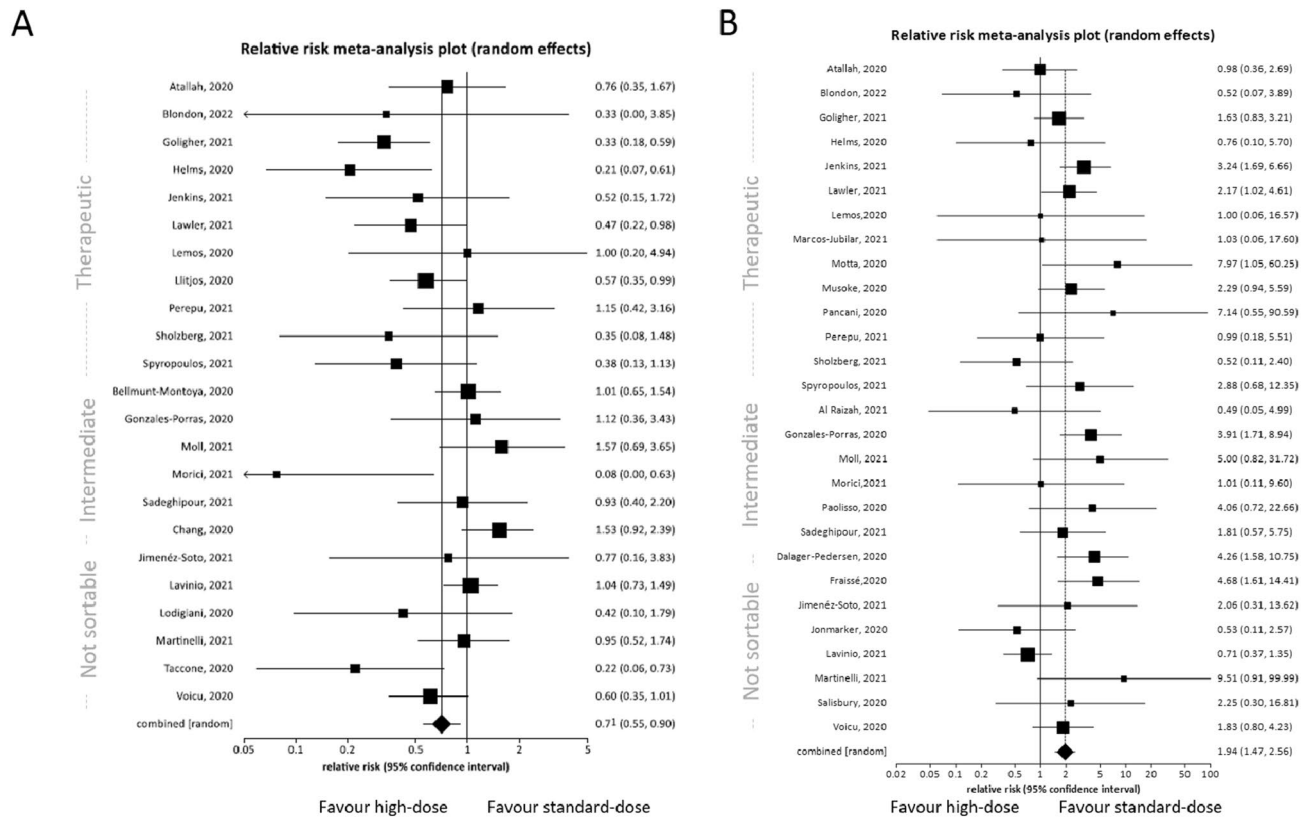

Fig. 1 Risk of venous thromboembolism (**A**) and major bleeding (**B**) in patients receiving high-dose or standard-dose heparin prophylaxis

0.68–1.03, I2 72.5%) (e-Fig. 4). Metaregression analyses showed no influence of study deign ($p = 0.968$), hospital setting ($p = 0.340$), study quality ($p = 0.836$), dose of heparin prophylaxis ($p = 0.693$) on heterogeneity.

Heterogeneity was reduced by excluding retrospective studies (RR 0.94, 95% CI 0.80–1.11, I2 32.1%) and remained unchanged after excluding low quality studies (RR 0.82, 95% CI 0.63–1.06, I2 79.2%). No differences were observed when subgroups by study design and clinical setting were analysed (Table 2, e-Table 3, e-Table 4, e-Fig. 5 and e-Fig. 6). In the non-ICU sub-analyses, heterogeneity persisted after exclusion of retrospective or low-quality studies, while in the ICU sub-analyses heterogeneity disappeared after the exclusion of retrospective studies (RR 1.04, 95% CI 0.92–1.16, I2 0.0%).

Egger's test revealed publication bias. Data on fatal PEs were reported in 3 studies and no events were observed in the two treatment groups. Fatal bleedings were higher in the high-dose regimen (0.28%) compared to the standard-dose heparin prophylaxis (0.04%) but the difference was not statistically significant (Table 2).

Discussion

This meta-analysis showed that in patients hospitalized with COVID-19, high-dose prophylactic heparin (intermediate or therapeutic) was associated with significantly lower rates of VTE (risk reduced by 29%) compared to standard-dose, with the trade off a significant increase of MB (risk increased by 51%). In particular, rates of MB were significantly doubled when heparin was used at therapeutic compared to standard prophylaxis doses. The efficacy to safety profile of high-dose heparin regimens expressed as LHH was lower in ICU patients than in non-ICU patients (0.9 and 1.6, respectively) in comparison to standard heparin prophylaxis. For the high-dose heparin regimens, a significant 52% risk reduction in VTE and a non-significant 55% risk increase in MB was observed for non-ICU patients, while a significant 30% risk reduction of VTE and a significant 53% risk increase of MB was observed in ICU patients. No significant differences were observed for all-cause-mortality.

A high incidence of thromboembolic complications was reported in patients hospitalized for COVID-19 that seemed to persist despite the use of standard heparin prophylaxis [1, 48]. Indeed, SARS-CoV-2 infection can induce excessive and aberrant hyper-inflammatory host immune response that is associated with a so-called

Table 2 Study outcomes according to study design and settings

	Studies; patients	High-dose* heparin prophylaxis %	Standard-dose heparin prophylaxis %	RR	95% CI	I2 %
Venous thromboembolism						
Overall	23; 8428	5.2	8.2	0.71	0.55–0.90	48.8
Randomized	9; 5130	1.8	4.0	0.51	0.35–0.74	9.5
Observational	14; 3298	13.7	11.5	0.81	0.62–1.05	49.2
ICU	15; 4000	8.8	11.6	0.70	0.52–0.93	52.1
Non-ICU	5; 3447	0.9	2.2	0.48	0.26–0.87	0.0
Major bleeding						
Overall	28; 10,283	4.2	2.2	1.94	1.47–2.56	18.1
Randomized	10; 5196	2.3	1.4	1.61	1.07–2.43	0.0
Observational	18; 5087	7.0	2.7	2.21	1.48–3.30	38.8
ICU	19; 5176	6.6	3.6	1.90	1.32–2.71	37.2
Non-ICU	7; 3528	1.7	0.9	1.82	0.98–3.36	0.0
All-cause death						
Overall	21; 7849	17.7	20.3	0.84	0.68–1.03	72.5
Randomized	10; 5204	17.2	18.7	0.91	0.76–1.10	39.1
Observational	11; 2645	19.0	22.7	0.80	0.53–1.19	81.7
ICU	13; 3494	30.9	30.5	0.79	0.63–1.00	64.8
Non-ICU	6; 3634	7.5	8.6	1.02	0.46–2.26	85.2
Fatal PE	3; 1329	0.0	0.0	–	–	–
Fatal bleeding	8; 4961	0.28	0.04	2.53	0.78–8.24	0.0

ICU intensive care unit, *PE* pulmonary embolism

*Therapeutic or intermediate heparin dose

"cytokine storm" and a prothrombotic derangement of the hemostatic system [2]. This condition is mainly described in patients with critical COVID-19 disease. A close interconnection between thrombosis and inflammation is well known [2]. The two processes mutually reinforce each other and the net effect of the excess of thrombin generation and fibrinolytic shutdown may induce a profound hypercoagulable state. These processes have been shown to result in diffuse microthrombosis and endotheliitis of pulmonary vessels in patient with severe COVID-19 [2, 49]. These events can be the basis for the disproportionately high incidence of overt thromboembolic events (DVT, PE overt and incidental subsegmental, arterial events) associated with COVID-19 despite the use of standard thromboprophylaxis [3]. Based on these data, many clinicians started to use increased doses of heparin to treat patients with COVID-19 and several studies have been conducted aimed at assessing the benefit of this approach. Indeed, international societies refrained physician from using high-dose heparin for prevention of thromboembolism in the lack of evidence from clinical trials [5].

Our meta-analysis shows that increasing heparin dose is associated with a reduction in VTE. However, this result is obtained at the cost of increased incidence of bleeding complications. Additionally, we observed a non-significant increase in fatal bleedings with high-dose heparin in comparison to standard heparin prophylaxis.

Overall, these results are not surprising. The concept that increasing anticoagulant effect results in bleeding is already known in many clinical scenarios as acute coronary syndromes, ischemic stroke and prophylaxis of VTE in medical patients [3, 50, 51]. Moreover, in patients admitted for COVID-19, those in the ICU setting have higher bleeding risks than those in the non-ICU setting [10–13].

A pre-COVID-19 Cochrane Review on the role of heparin prophylaxis in more than 7,000 acute medical patients showed a 0.6% incidence of major bleeding with the use of heparin prophylaxis [51]. This rate is similar to that observed in our meta-analysis in non-ICU patients receiving standard heparin dose (0.9%). In our meta-analysis non-ICU patients seemed to receive the best risk reduction (52%) in VTE from high-dose heparin regimen, despite a quite low absolute event rate (2.2%) and at no significant increase in MB.

We observed no effect of high-dose vs. standard-dose of heparin in mortality in hospitalized patients for COVID-19. This result is clinically relevant as the majority of randomized studies assessing the efficacy and safety of the two heparin regimens had death or duration of need for organ support and not VTE as primary outcome. The

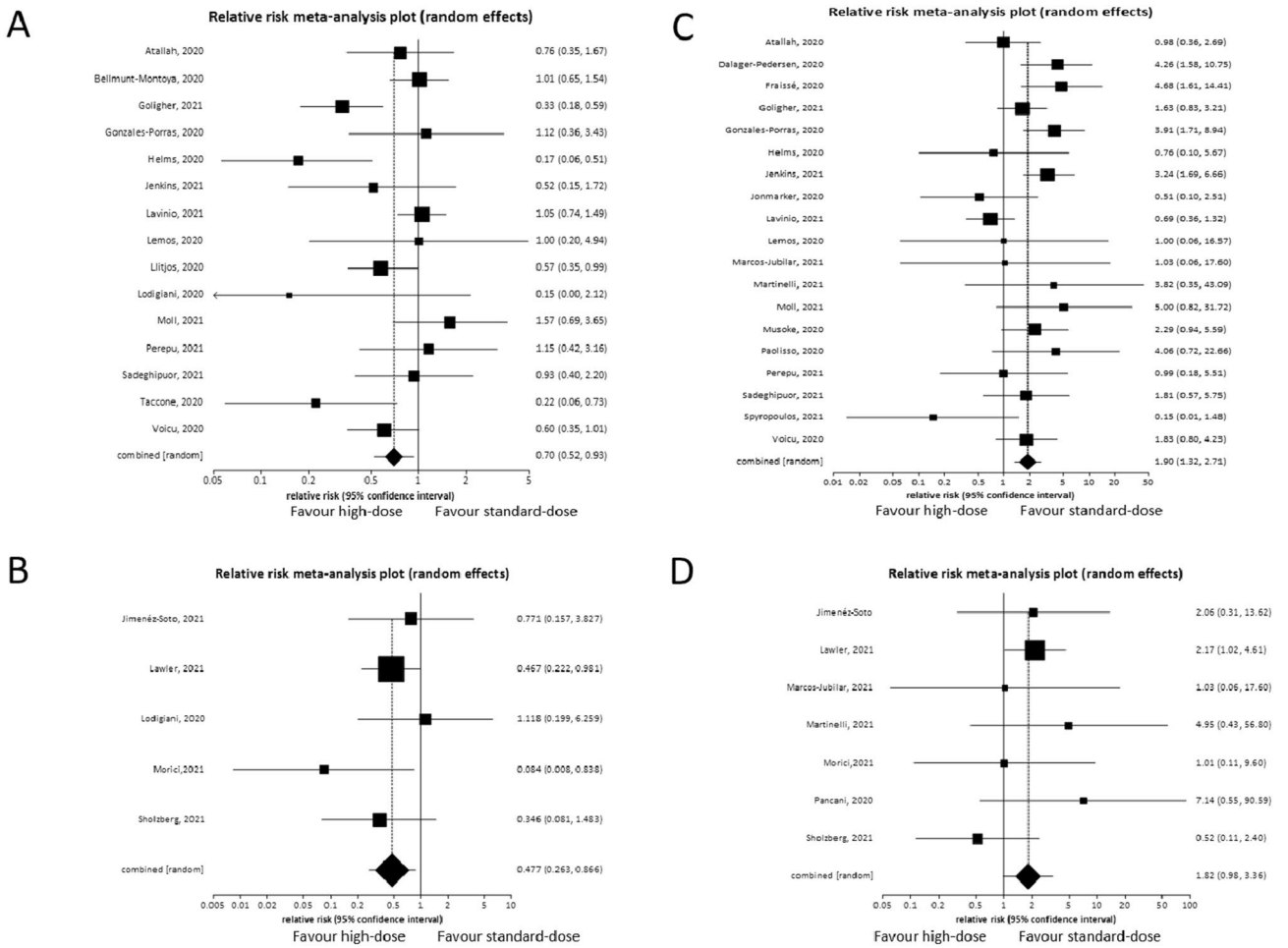

Fig. 2 Risk of venous thromboembolism (**A** = ICU; **B** = non-ICU) and major bleeding (**C** = ICU; **D** = non-ICU) in patients receiving high-dose or standard-dose heparin prophylaxis according to hospital setting

rationale for this outcome is based on the concept that prevention of microthrombosis could prevent refractory ARDS and death. However, meta-analyses focused on mortality outcome showed controversial results. Parisi et al. reported an advantage of the therapeutic anticoagulation compared with the prophylactic anticoagulation especially in patients admitted to ICU (RR 0.30, 95% CI 0.15–0.60), while Ortega-Paz et al. showed no differences in all-cause death between the two heparin regimens (RR 0.96, 95% CI 0.78–1.18) [52, 53]. Some points should be underlined: in the first meta-analysis no RCTs were included, while the second consisted of only RCTs counting also a recent study comparing therapeutic rivaroxaban or heparin to standard-dose heparin prophylactic anticoagulation.

Differently from previous meta-analyses we focused on VTE as primary outcome and performed a strict selection of studies excluding those reporting on anticoagulants different from heparin. This may have led to a selection of a sicker population; however, the main findings were confirmed in the sub-analyses of the RCTs.

In our study, despite the beneficial effect of high-dose prophylactic heparin in preventing VTEs, no advantage on mortality was observed and a safety concern raised. This finding is in keeping with recent findings from three large RCTs. The first study by Sadeghipour et al. showed a not significant difference in the primary outcome (venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality) and no difference in VTE events when assessed separately in patients admitted to ICU who received heparin at intermediate dose compared to standard prophylaxis [10]. Similarly, Goligher et al. found that patients in the ICU setting who received therapeutic anticoagulation with heparin did not have a greater probability of organ support free days or survival compared to those receiving usual care pharmacologic thromboprophylaxis [11]. As expected, major thrombotic and PE events were reduced (6.4% vs 10.4%, and 2.5% vs 7.5%, respectively)

and major bleedings increased (3.8% vs 2.3%) in patients who received therapeutic compared to those receiving standard heparin thromboprophylaxis. Interestingly, in patients in the non-ICU setting, therapeutic anticoagulation with heparin increased the probability of survival without organ support as compared with usual care thromboprophylaxis [12]. Major thrombotic events and PEs were reduced (1.1% vs 2.1%, and 0.9% vs 1.8%, respectively) with a not significant increase in the risk of MB (1.9% vs 0.9%) in patients receiving therapeutic heparin doses as compared with usual care thromboprophylaxis. Differently, in the study by Spyropoulos et al. therapeutic-dose LMWH reduced major thromboembolism and death (RR 0.68, 95% CI, 0.49–0.96) compared with standard heparin thromboprophylaxis in hospitalized patients with COVID-19 (but not in ICU patients) [13]. However, patients could have been included in case of very elevated D-dimer levels and only 257 patients were included out of the 11,694 screened (548 declined participation in the study).

Our results are in line with those of Valeriani et al. [54]. Differently from that meta-analysis we included both observational and RCTs. We believe our findings can increase knowledge on this topic and extend the results of previous studies including only RCTs. Indeed, previous meta-analyses on RCTs only, have reported conflicting results. For example, the use of full dose anticoagulation was suggested regardless of clinical setting in the study by Loffredo et al. [55], while it was discouraged by Sholzberg et al. [56] in critically ill patients.

Our study has some limitations in addition to those intrinsic to the meta-analytic approach, which combines heterogeneous datasets. First, the definition of standard thromboprophylaxis is heterogeneous among studies. In some studies [10–13, 20, 26, 30, 34, 40, 42] for a small number of patients, standard-heparin doses were adjusted in case of high body weight or BMI. In particular, in one study by the multiplatform [11] many patients in the standard-heparin group actually received intermediate-dose thromboprophylaxis upon admission to the ICU due to a change in the national (United Kingdom) practice guidelines during the trial. However, when this study was removed from our main analysis, results remained unchanged (e-Table 2). Similarly, no differences were observed with the main findings in the sub-analyses were data from the HEP-COVID trial were excluded [13]. In that study, 39% of the patients assigned to the standard heparin group received the intermediate-dose heparin prophylaxis. Second, as this is an aggregated data meta-analysis no adjustment for age, comorbidities and severity of disease, concomitant treatments were performed. Third, high heterogeneity was observed in the majority of the analyses on death, but this result should be regarded by taking into account the multiple causes of death, about 30% of these patients died due to respiratory failure and 30% due to sepsis. Moreover, in the VTE study outcome, metaregression analysis showed influence of heparin prophylaxis on heterogeneity. Indeed, in the separate analyses on intermediate and on therapeutic doses no heterogeneity was observed. Fourth, the open-label design may have introduced bias in the ascertainment of thrombotic events in the RCTs. Fifth, the search strategy may not be complete as some databases have been lost (eg EMBASE). However, references of the included studies were selected and only one study was found and added to the meta-analysis. At last, publication bias could not be excluded for mortality outcome, indeed study selection was focused on studies reporting VTE and bleeding events.

Some strengths of this meta-analysis that should be underlined include the following : (i) the selection of studies using heparin as thromboprophylaxis treatment; (ii) the focus on VTE as primary outcome; (iii) the high number of included studies and patients; (iv) the inclusion of the recently published RCTs; (v) the subgroups analyses of the different settings (ICU and non-ICU); (vi) additional data on fatal PEs and on fatal bleedings.

Conclusion

The use of heparin prophylaxis at high-dose reduces the risk of VTE but increased the risk of MB compared to the standard-dose. No clinical benefit for heparin high-dose was observed for ICU setting, but its role in the non-ICU should be further evaluated.

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Data Availability The database is available on reasonable request to the corresponding author.

Declarations

Conflict of interest M.C.V and M.G. have no conflicts to declare. G.A. reports receiving personal fees from Bristol Myers Squibb, Bayer HealthCare, and Daiichi Sankyo, outside the submitted work. C.B. reports receiving personal fees from Bayer HealthCare, Bristol Myers Squibb, and Daiichi Sankyo, outside the submitted work.

Ethical Statements Not applicable.

Human and animal rights Not needed since this study did not involve any human or animal.

Informed consent Not applicable.

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