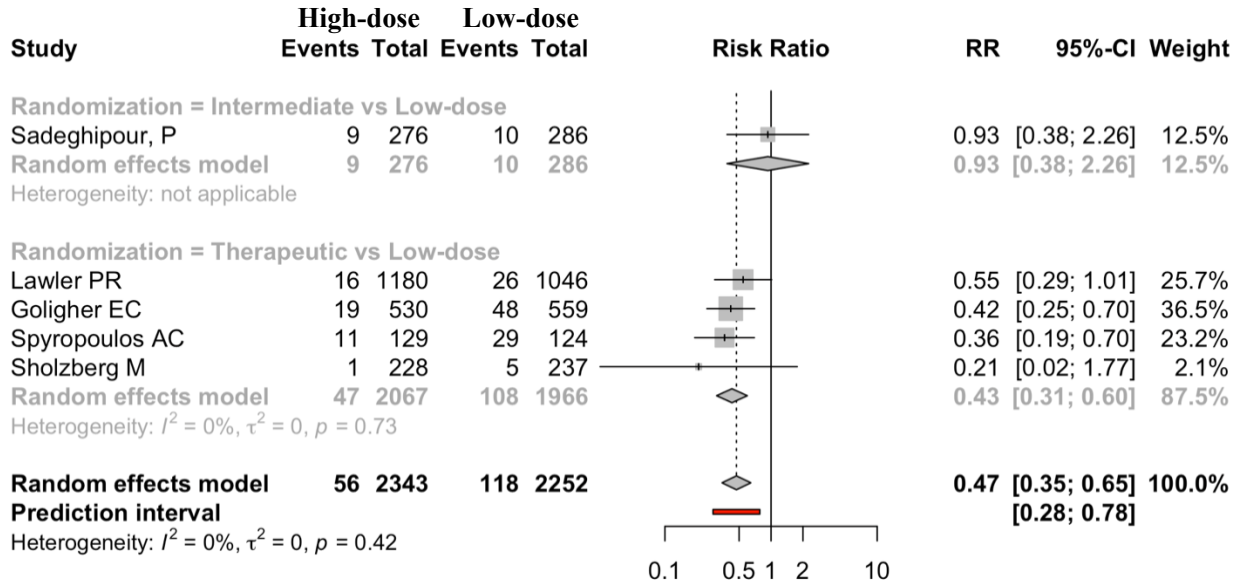
Supplementary material

Supplementary Table 1. Complete search strategy

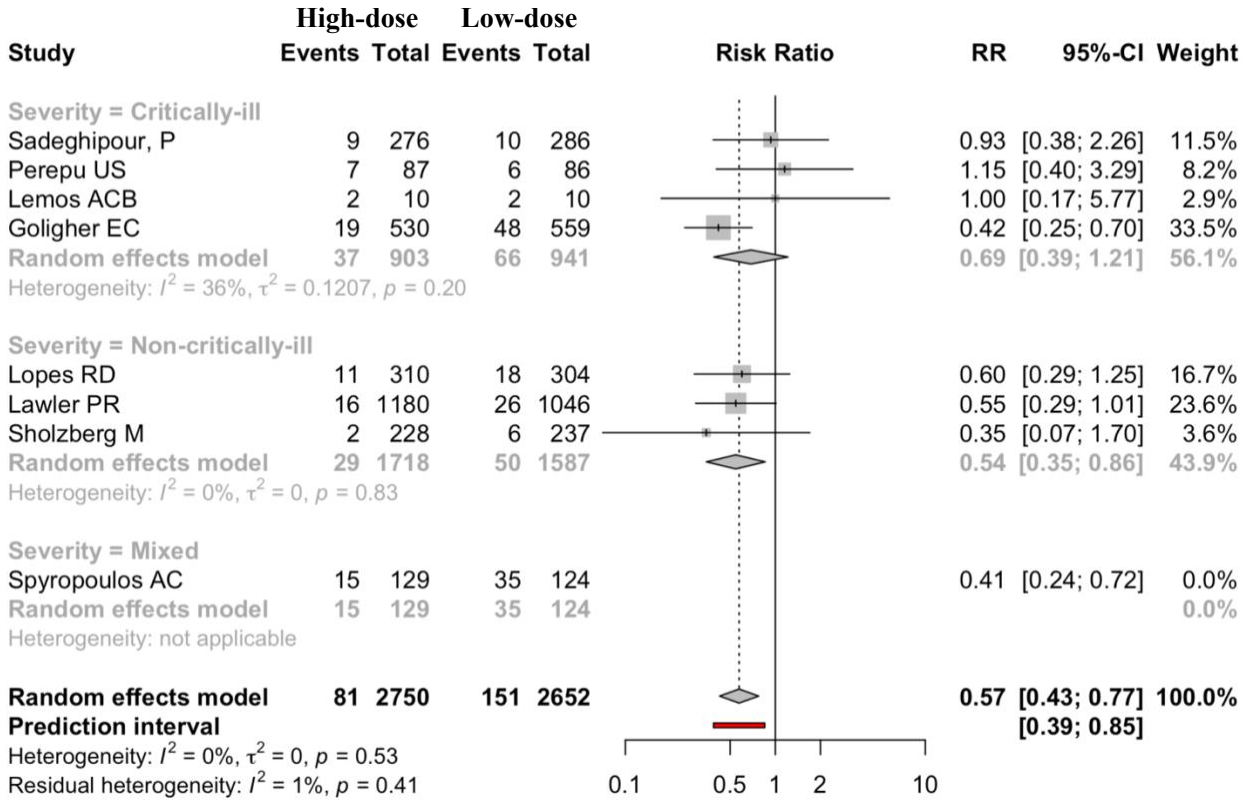
Date of the search	October 2021
Time period considered	from inception to October 2021
Search strategy	1 - coronavirus disease 2019'/exp OR 'coronavirus disease 2019' 2 - venous thromboembolism 3 - vein thrombosis 4 - lung embolism 5 - anticoagulant agent 6 - heparin 7 – low molecular weight heparin 8 - acenocumarol 9 - warfarin 10 – antivitamin k 11 - rivaroxaban 12 - apixaban 13 – dabigatran etexilate 14 - edoxaban 15 – 1 OR 2 OR 3 OR 4 16 – 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 17 – 15 AND 16 18 – 17 AND randomized controlled trial/de

Supplementary Figure 1. Symptomatic venous thromboembolism in hospitalized patients with COVID-19 sorted by dose of anticoagulation in the experimental arm



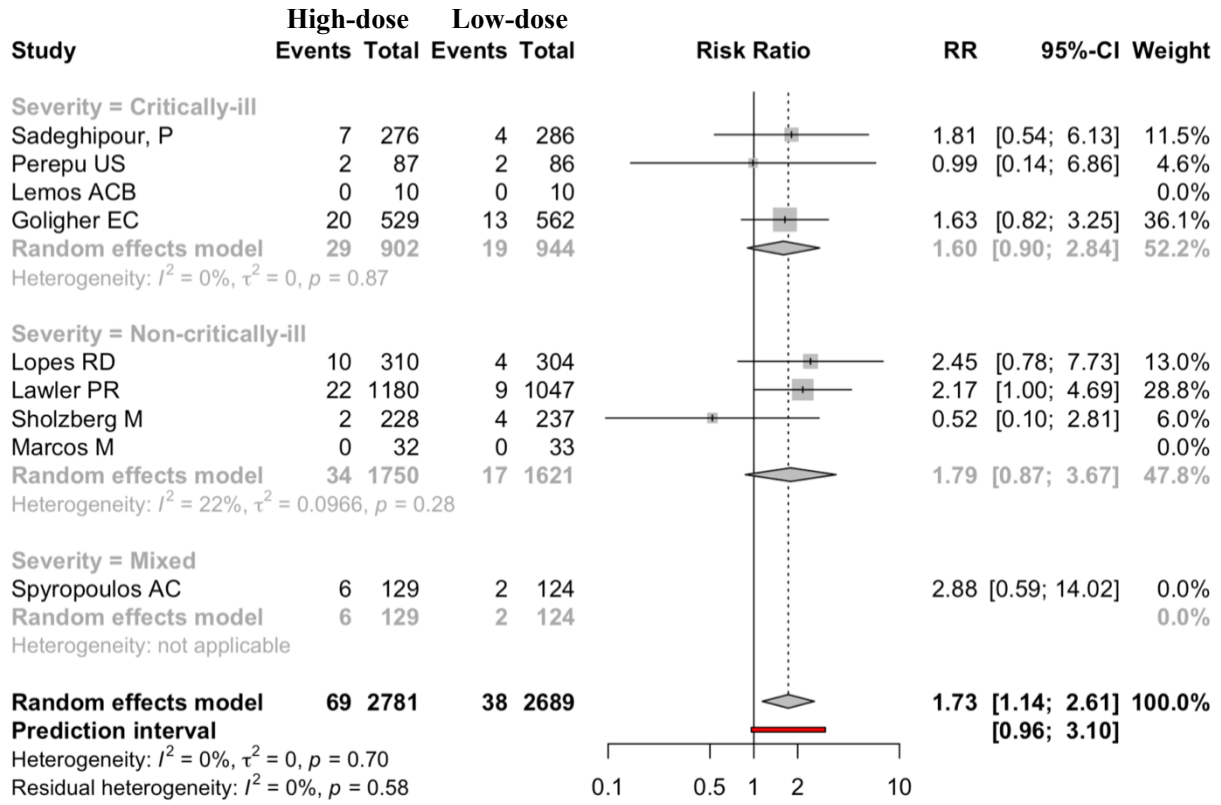
p-value for subgroup difference = 0.11
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 2. Venous thromboembolism in hospitalized patients with COVID-19 sorted by disease severity



p-value for subgroup difference = 0.53
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 3. Major bleeding in hospitalized patients with COVID-19 sorted by disease severity

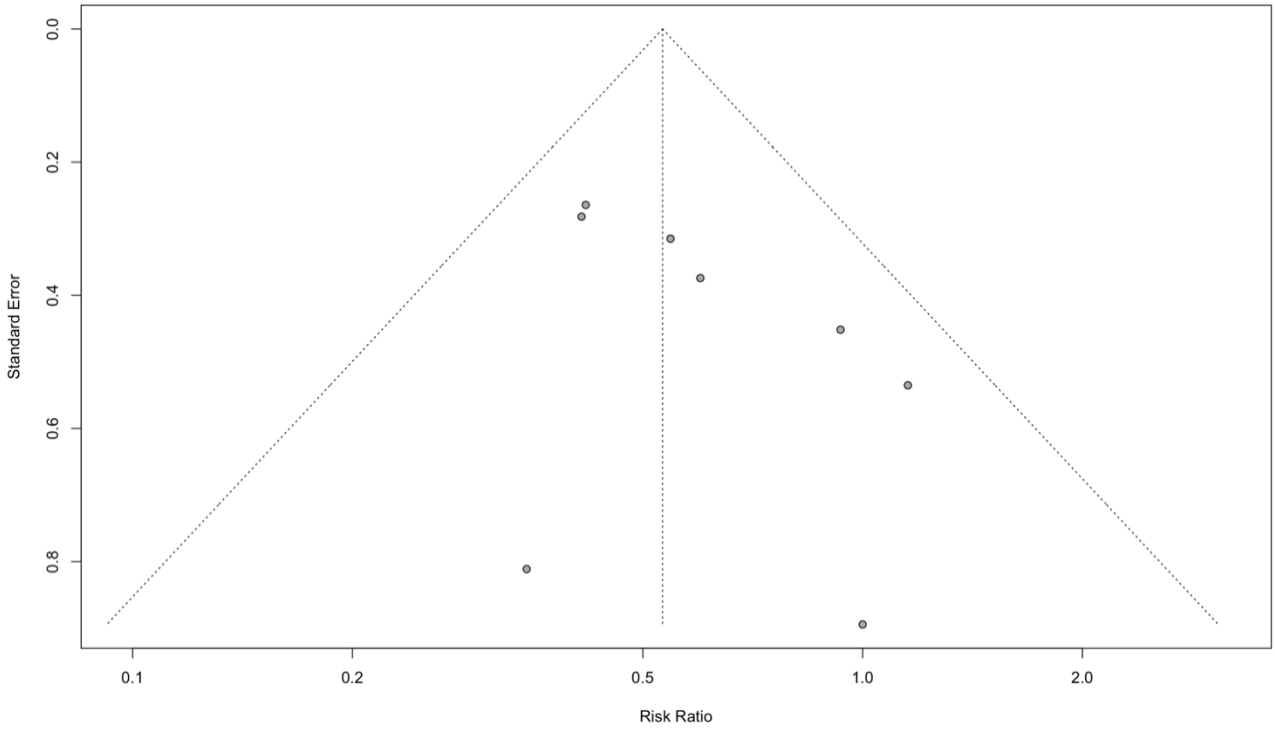


p-value for subgroup difference = 0.81

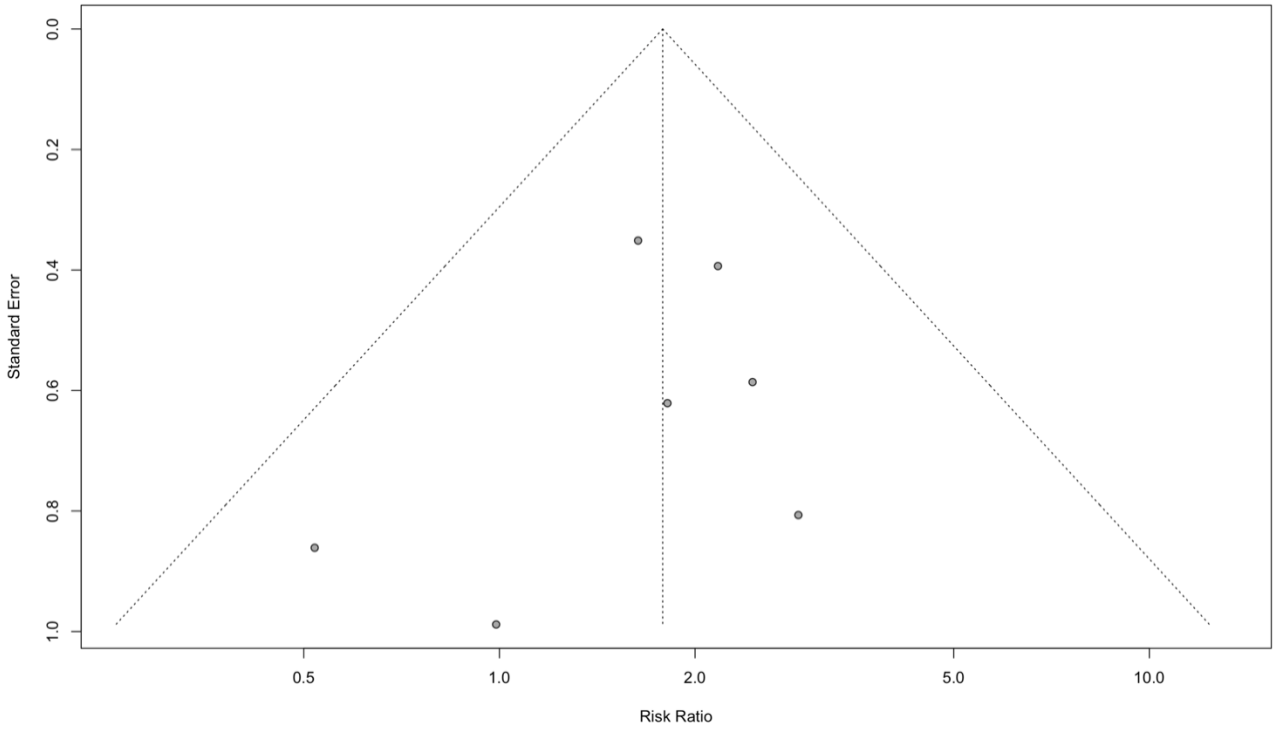
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.

CI, Confidence interval; RR = risk ratio

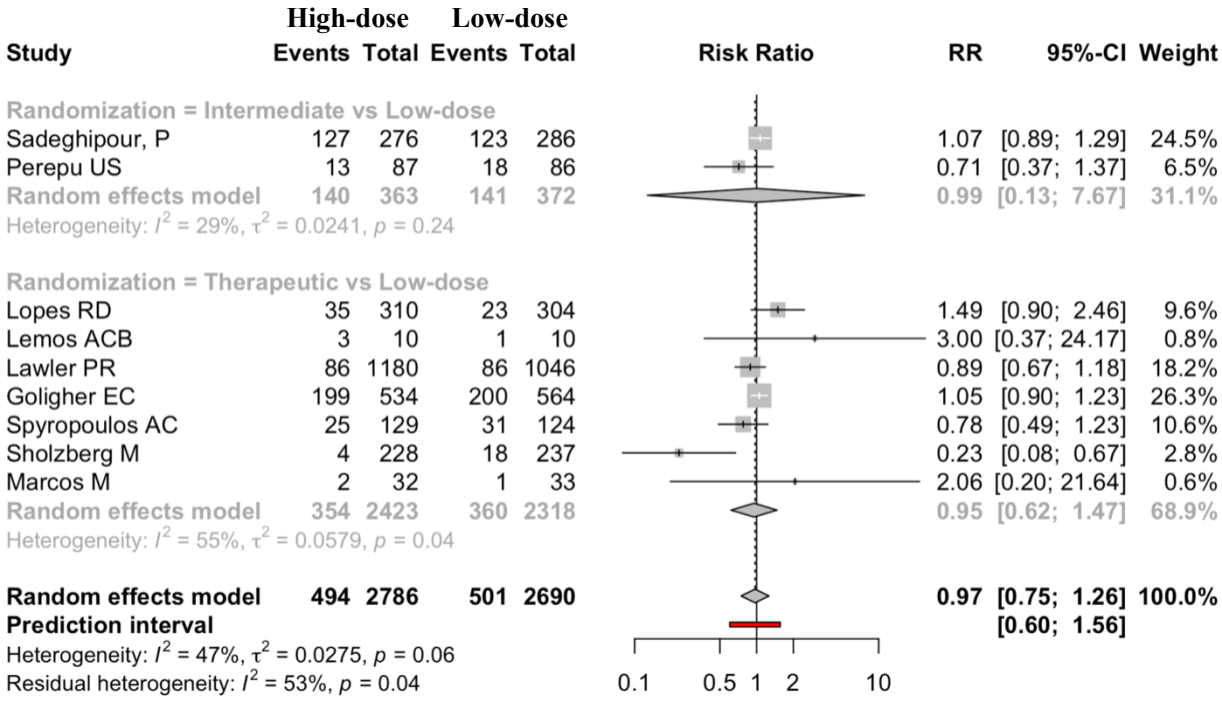
Supplementary Figure 4. Funnel plot for venous thromboembolism



Supplementary Figure 5. Funnel plot for major bleeding



Supplementary Figure 6. All-cause mortality in hospitalized patients with COVID-19 sorted by dose of anticoagulation in the experimental arm

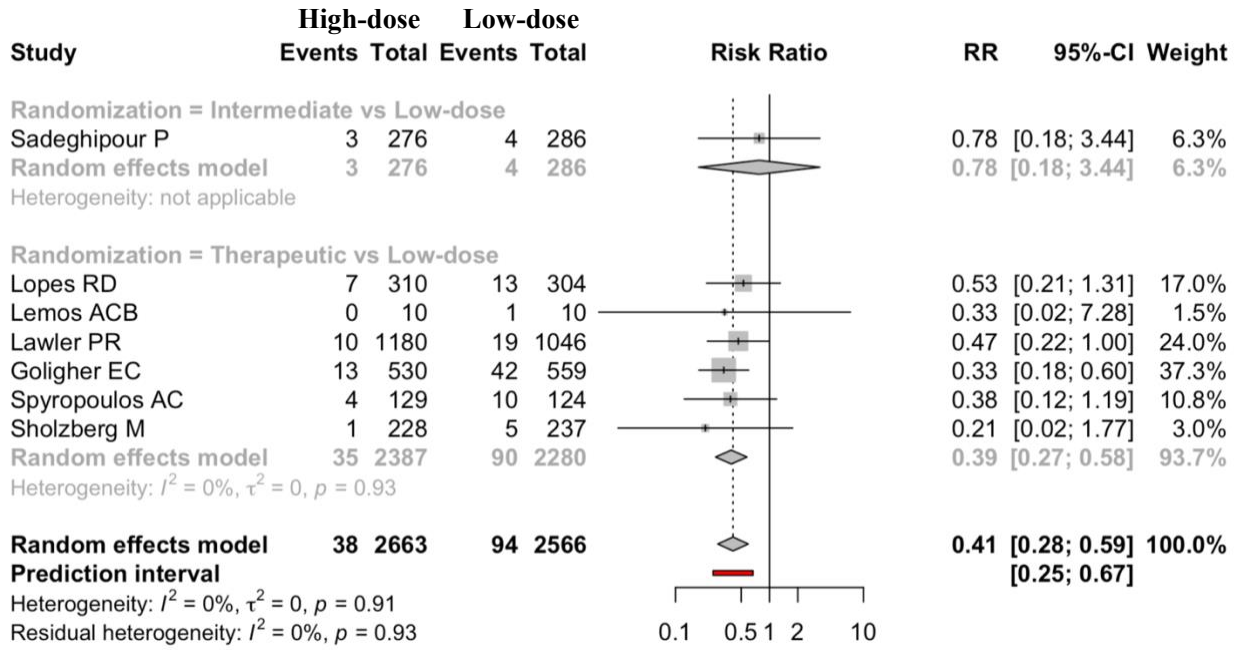


p-value for subgroup difference = 0.88

Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.

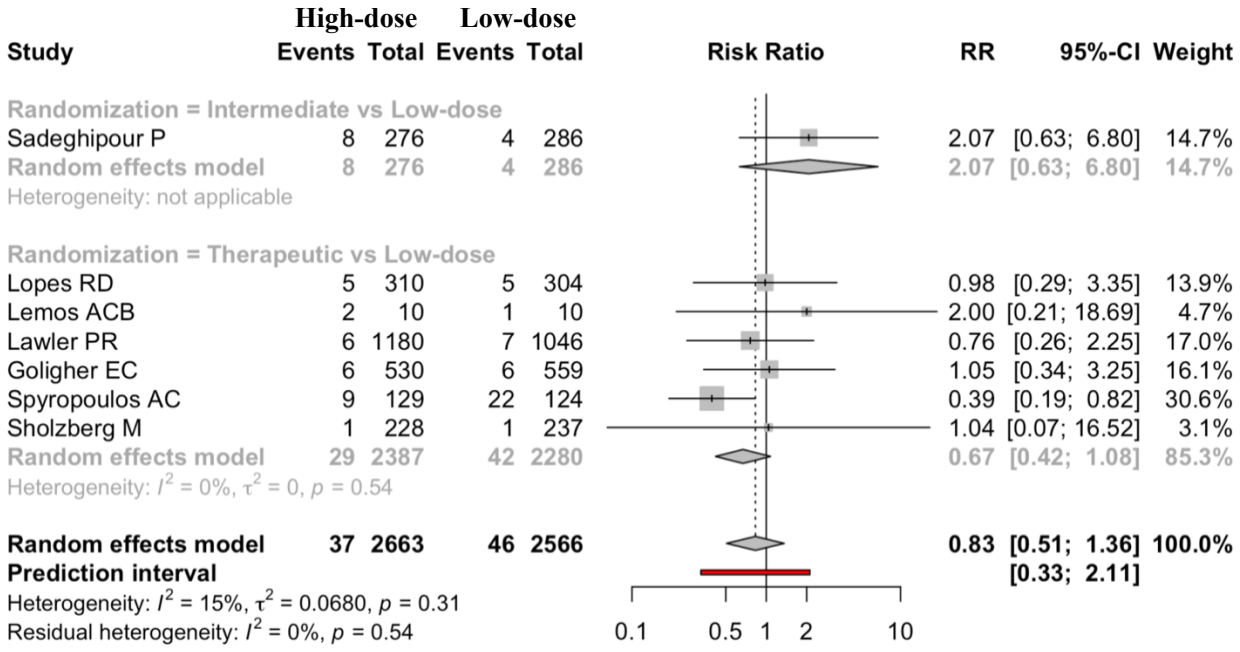
CI, Confidence interval; RR = risk ratio

Supplementary Figure 7. Pulmonary embolism in hospitalized patients with COVID-19



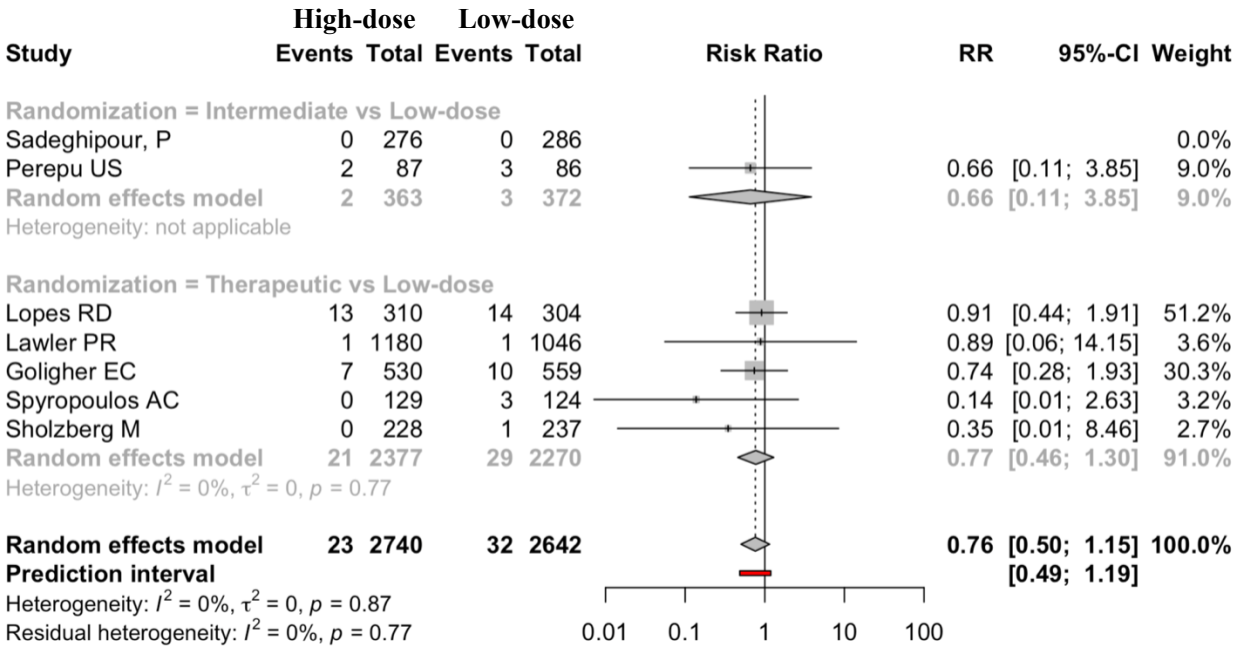
p-value for subgroup difference = 0.38
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 8. Deep vein thrombosis in hospitalized patients with COVID-19



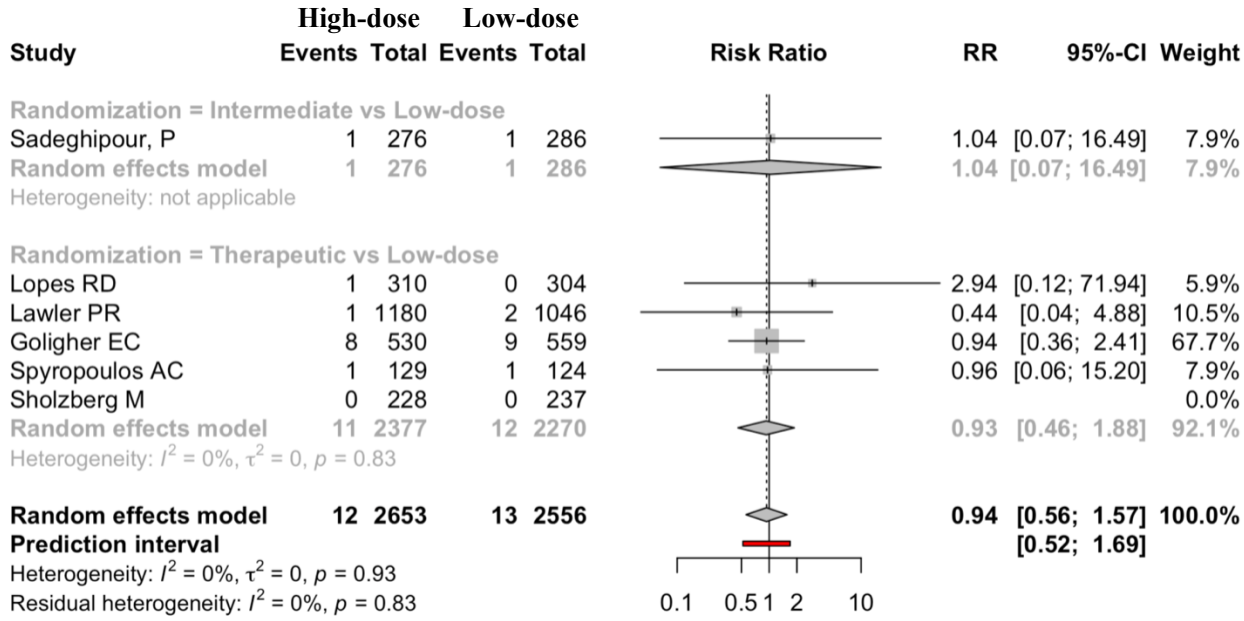
p-value for subgroup difference = 0.08
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 9. Acute myocardial infarction in hospitalized patients with COVID-19



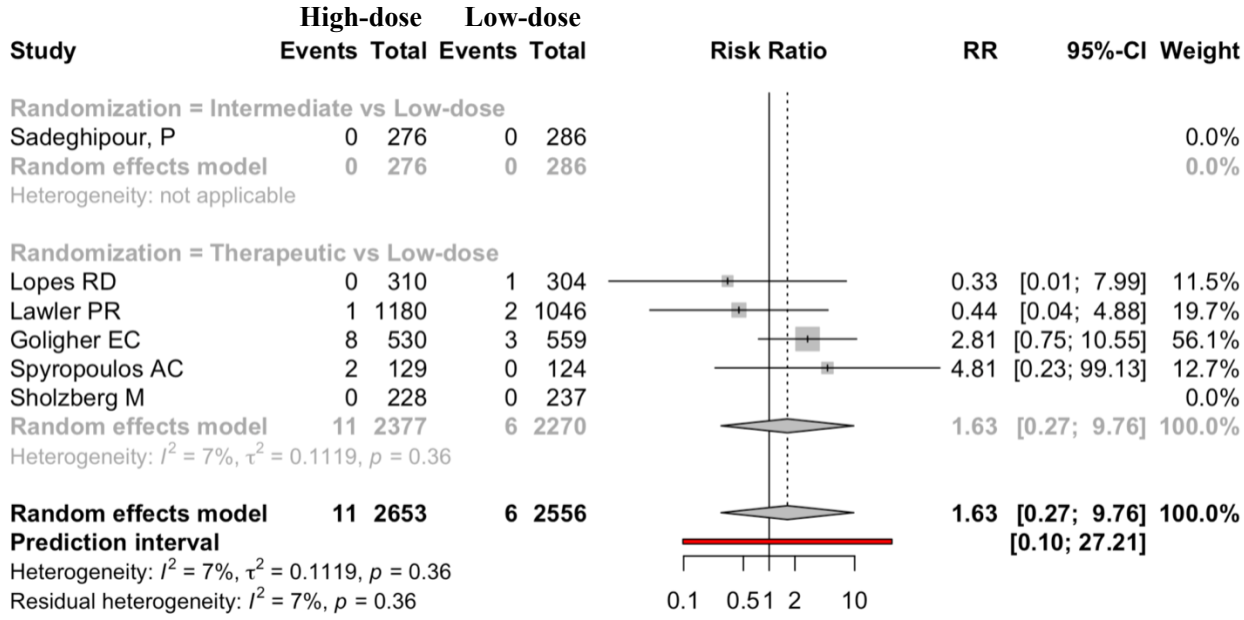
p-value for subgroup difference = 0.86
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 10. Acute ischemic stroke in hospitalized patients with COVID-19



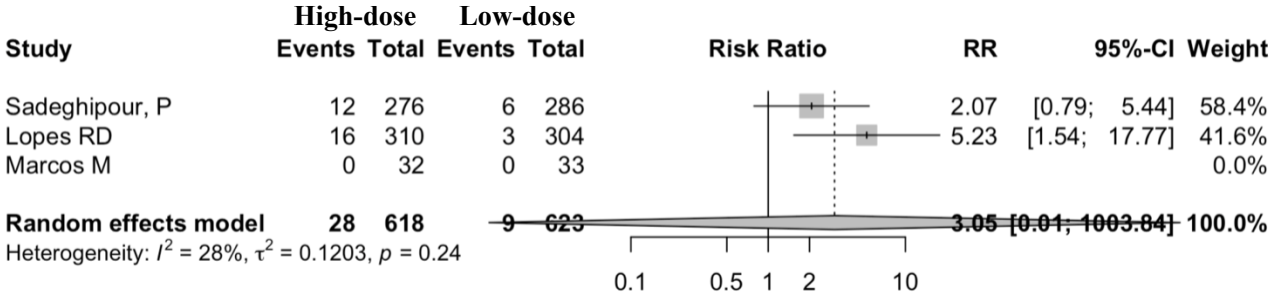
p-value for subgroup difference = 0.94
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 11. Acute peripheral arterial ischemic events in hospitalized patients with COVID-19



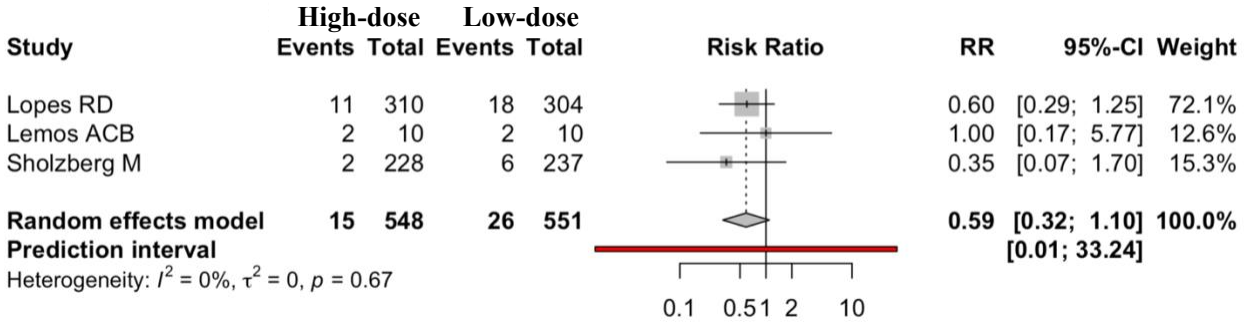
p-value for subgroup difference, not applicable
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 12. Clinically relevant non-major bleeding in hospitalized patients with COVID-19



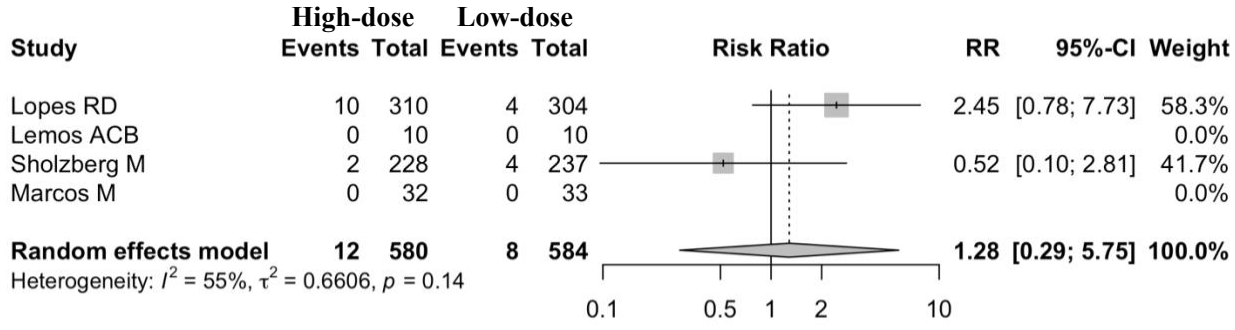
CI, Confidence interval; RR = risk ratio

Supplementary Figure 13. Venous thromboembolism in patients receiving the intended high-dose or low-dose thromboprophylaxis



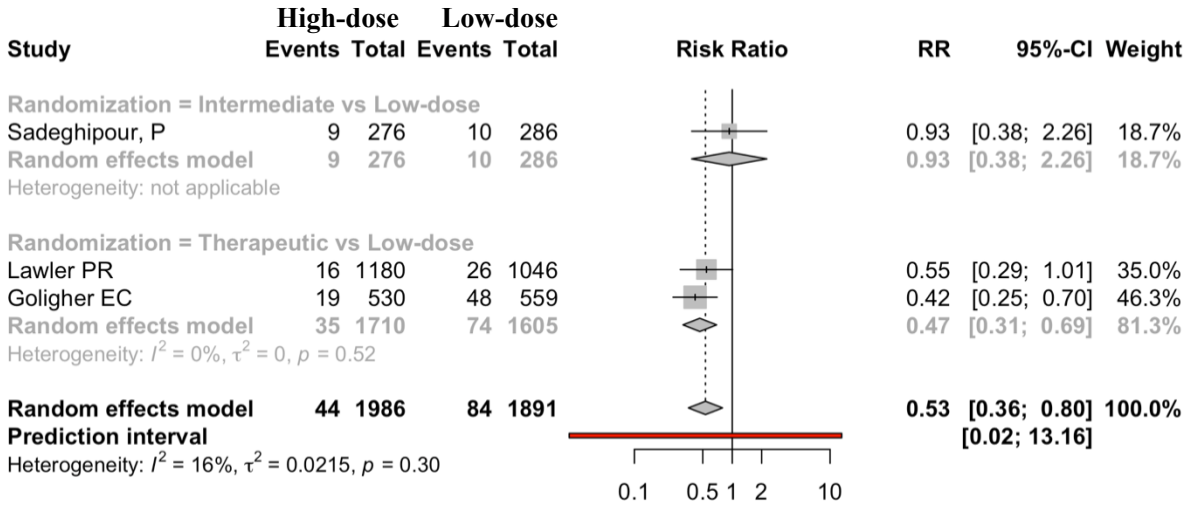
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 14. Major bleeding in patients receiving the intended high-dose or low-dose thromboprophylaxis



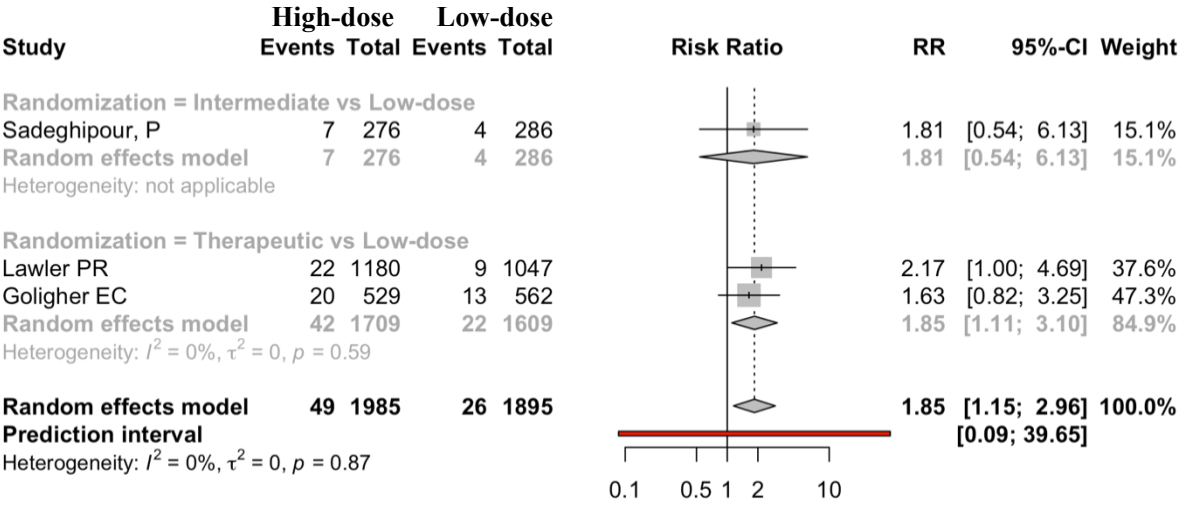
CI, Confidence interval; RR = risk ratio

Supplementary Figure 15. Venous thromboembolism in patients admitted to intensive care unit



p-value for subgroup difference = 0.16
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Supplementary Figure 16. Major bleeding in patients admitted to intensive care unit



p-value for subgroup difference = 0.27
Prediction interval shows the extent of between-study variation and predict the possible effect in a future study that is comparable to those included in the meta- analysis.
CI, Confidence interval; RR = risk ratio

Summary of findings table

Outcomes	Relative effect (95% CI)	Difference (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	What it means
Venous thromboembolism	RR 0.53 (0.41 to 0.69)	27 per 1000 fewer events (17 fewer to 38 more)	5402 (8)	⊕⊕⊕⊖ **Moderate[a]**	High-dose thromboprophylaxis reduces the risk of venous thromboembolism
Major bleeding	RR 1.78 (1.20 to 2.66)	11 per 1000 more events (3 more to 17 more)	5470 (9)	⊕⊕⊕⊖ **Moderate[a]**	High-dose thromboprophylaxis increaased the risk of major bleeding

[a]Downgraded one level because of the risk of bias - deviation from intended intervention -
CI, confince interval

Protocol of the systematic review and meta-analysis

Review title	High-dose versus low-dose venous thromboprophylaxis in hospitalized patients with COVID-19: a systematic review and meta-analysis
Original language title	English
Anticipated or actual start date	01/09/2021
Anticipated completion date	31/12/2021

Review team details

Review team members & their organisational affiliations	Dr. E. Valeriani, Department of Public Health and Infectious Diseases, Sapienza University of Rome Dr. Angelo Porfidia, Department of Medicine, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore School of Medicine, Rome, Italy Prof Walter Ageno, Department of Medicine and Surgery, University of Insubria, Varese, Italy Dr. Silvia Spoto, Diagnostic and Therapeutic Medicine Department, University Campus Bio-Medico of Rome, Italy Roberto Pola PhD, Department of Medicine, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore School of Medicine, Rome, Italy Marcello Di Nisio, Department of Medicine and Ageing Sciences, University "G. d'Annunzio" of Chieti-Pescara, Chieti, Italy
12. Funding sources/sponsors	None
13. Conflicts of interest	E. Valeriani and S. Spoto have nothing to disclose. A. Porfidia reports personal fees from Bayer, Boehringer Inghelheim, Daiichi Sankyo, BMS-Pfizer, Novartis and Aspen, outside the submitted work. W. Ageno reports grants and personal fees from Bayer, and personal fees from BMS/Pfizer, Daiichi Sankyo, Sanofi, Aspen, Janssen, and Portola, outside the submitted work. R. Pola reports personal fees from Bayer, Boehringer Inghelheim, Daiichi Sankyo, BMS-Pfizer, Novartis and Aspen, outside the submitted work. M. Di Nisio reports personal fees from Bayer, Daiichi Sankyo,

	BMS-Pfizer, Leo Pharma, Sanofi, and Aspen, outside the submitted work.

Review methods

Review question(s)	Is High-dose venous thromboprophylaxis more effective and safe than low-dose venous thromboprophylaxis in hospitalized patients with COVID-19
Searches	We will perform a systematic search using the electronic databases MEDLINE and Embase from January 2020 up to October 2021 without any restrictions.
Participants/ population	Hospitalized patients with COVID-19
Intervention(s), exposure(s)	High-dose venous thromboprophylaxis
Comparator(s)/ control	Low-dose venous thromboprophylaxis
Types of study to be included	Randomized controlled trials
Main outcome(s)	The primary efficacy outcome will be the occurrence of any symptomatic or incidental VTE. The primary safety outcome will be major bleeding as defined by the authors
Additional outcomes	The secondary efficacy outcomes will be all-cause mortality, acute myocardial infarction, acute ischemic stroke, acute peripheral arterial ischemic events, symptomatic or incidental deep vein thrombosis, and symptomatic or incidental pulmonary embolism. The secondary safety outcomes will be clinically relevant non-major bleeding and heparin-induced thrombocytopenia.
Data extraction, (selection and coding)	Two authors will perform study selection and data extraction independently, with disagreements solved through discussion with a third author. The following data will be extracted from full-text studies: study characteristics (e.g., number of included patients, health-care setting), patient characteristics (e.g., age, sex, presence of comorbidities, disease severity), anticoagulant regimens in both experimental and control groups (e.g., type, dose, and duration of anticoagulation), number of patients who experienced the outcome of interest, and follow-up duration.
Risk of bias (quality) assessment	Two authors will assess study quality independently using the revised Cochrane risk-of-bias tool for randomized trials

Strategy for data synthesis	Categorical variables will be described as counts and percentages and continuous variables presented as median (interquartile range) or mean (standard deviation), as appropriate. Pooled risk ratios (RRs) with corresponding 95% confidence intervals (CIs) and prediction intervals (PIs) will be calculated using a random-effects model. The number of patients needed to treat to prevent one thrombotic event or to provoke one major bleeding and absolute measure of effect will be calculated respectively for primary efficacy and safety outcomes in case of statistically significant findings.
Analysis of subgroups or subsets	Sensitivity analyses will be performed to compare the efficacy and safety of intermediate or therapeutic dose versus low-dose thromboprophylaxis, and of high-dose versus low-dose thromboprophylaxis in critically-ill and non-critically-ill COVID-19 patients.