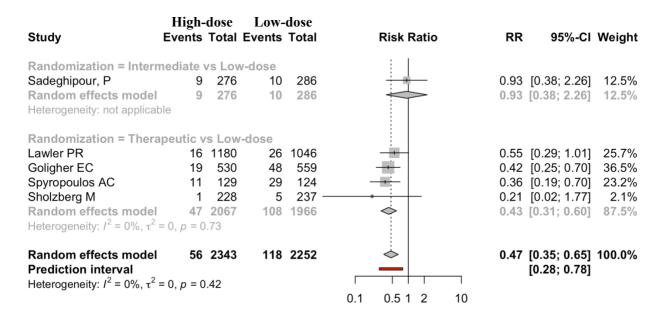
Supplementary material

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 |

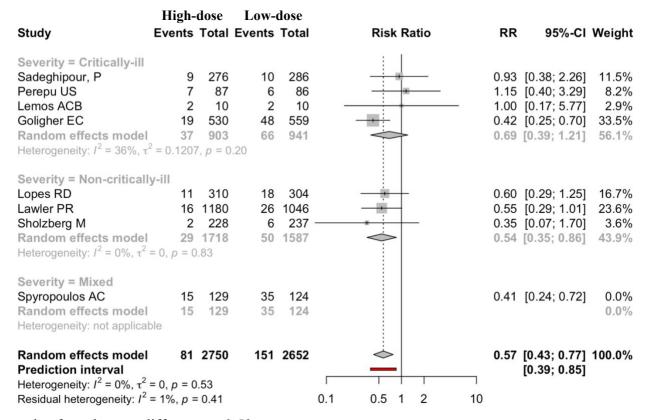
Supplementary Figure 1. Symptomatic venous thromboembolism in hospitalized patients with COVID-19 sorted by dose of anticoagulation in the experimental arm



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.

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.

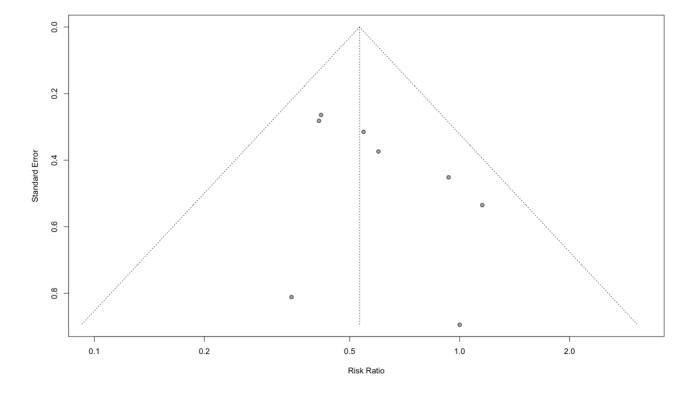
Supplementary Figure 3. Major bleeding in hospitalized patients with COVID-19 sorted by disease severity

| Study | High-dose Events Total E | Low-dose vents Total | Risk Ratio | RR 95%-CI Weight |
|---|--|---|--------------|---|
| Severity = Critically-ill Sadeghipour, P Perepu US Lemos ACB Goligher EC Random effects model Heterogeneity: $I^2 = 0\%$, τ^2 | 7 276 2 87 0 10 20 529 29 902 = 0, p = 0.87 | 4 286 2 86 0 10 13 562 19 944 | | 1.81 [0.54; 6.13] 11.5% 0.99 [0.14; 6.86] 4.6% 0.0% 1.63 [0.82; 3.25] 36.1% 1.60 [0.90; 2.84] 52.2% |
| Severity = Non-critically Lopes RD Lawler PR Sholzberg M Marcos M Random effects model Heterogeneity: $I^2 = 22\%$, τ^2 | 10 310 22 1180 2 228 0 32 34 1750 | 4 304 9 1047 4 237 - 0 33 17 1621 | * | 2.45 [0.78; 7.73] 13.0% 2.17 [1.00; 4.69] 28.8% 0.52 [0.10; 2.81] 6.0% 0.0% 1.79 [0.87; 3.67] 47.8% |
| Severity = Mixed Spyropoulos AC Random effects model Heterogeneity: not applicate | 6 129 6 129 | 2 124 2 124 | | 2.88 [0.59; 14.02] 0.0% 0.0% |
| Random effects model Prediction interval Heterogeneity: $I^2 = 0\%$, τ^2 Residual heterogeneity: I^2 | | 38 2689 0. | 1 0.5 1 2 10 | 1.73 [1.14; 2.61] 100.0% [0.96; 3.10] |

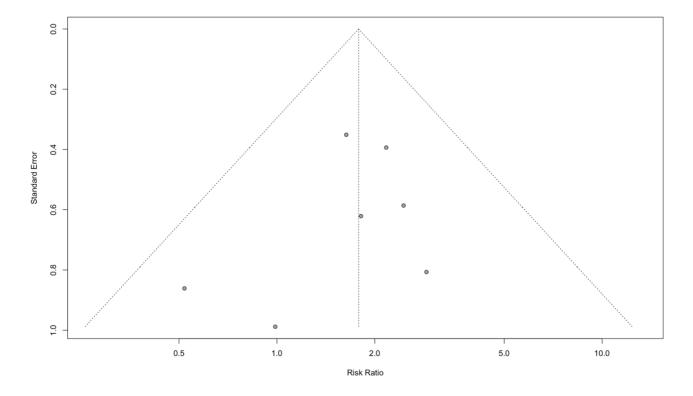
p-value for subgroup difference = 0.81

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.

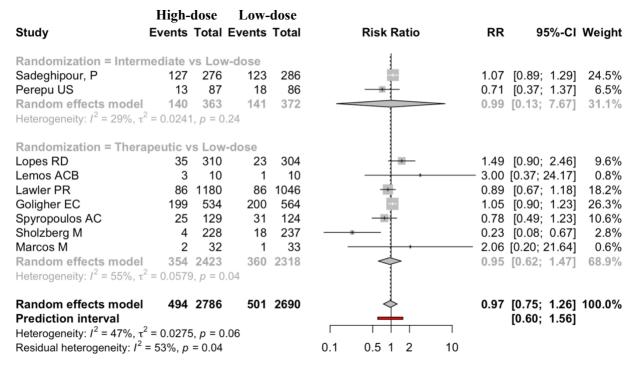
Supplementary Figure 4. Funnel plot for venous thromboembolism



Supplementary Figure 5. Funnel plot for major bleeding



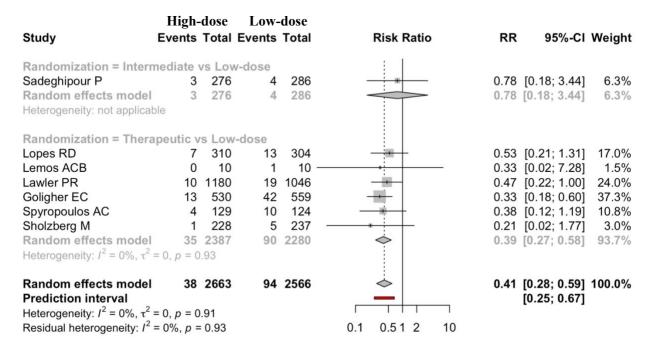
Supplementary Figure 6. All-cause mortality in hospitalized patients with COVID-19 sorted by dose of anticoagulation in the experimental arm



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.

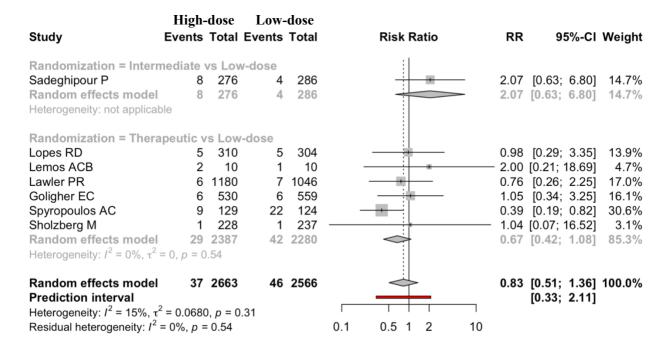
Supplementary Figure 7. Pulmonary embolism in hospitalized patients with COVID-19



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.

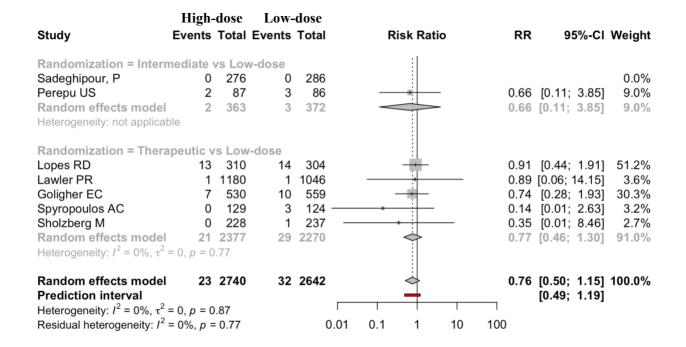
Supplementary Figure 8. Deep vein thrombosis in hospitalized patients with COVID-19



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.

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.

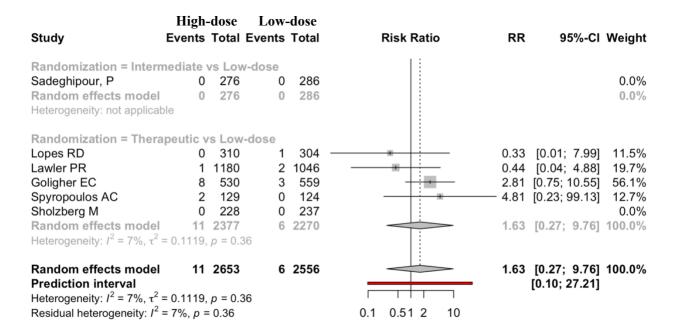
Supplementary Figure 10. Acute ischemic stroke in hospitalized patients with COVID-19

|] | High- | dose | Low- | dose | | | |
|---|---------|--------|--------|-------|--------------------|---------------|---------------------|
| Study Ev | ents | Total | Events | Total | Risk Ratio | RR | 95%-CI Weight |
| Randomization = Intermed | diate v | /s Low | v-dose | | 1 | | |
| Sadeghipour, P | 1 | 276 | 1 | 286 | | 1.04 | [0.07; 16.49] 7.9% |
| Random effects model | 1 | 276 | 1 | 286 | | 1.04 | [0.07; 16.49] 7.9% |
| Heterogeneity: not applicable | | | | | | | |
| Randomization = Therape | utic v | s Low | -dose | | | | |
| Lopes RD | 1 | 310 | 0 | 304 | | — 2.94 | [0.12; 71.94] 5.9% |
| Lawler PR | 1 | 1180 | 2 | 1046 | | 0.44 | [0.04; 4.88] 10.5% |
| Goligher EC | 8 | 530 | 9 | 559 | | 0.94 | [0.36; 2.41] 67.7% |
| Spyropoulos AC | 1 | 129 | 1 | 124 | + | 0.96 | [0.06; 15.20] 7.9% |
| Sholzberg M | 0 | 228 | 0 | 237 | | | 0.0% |
| Random effects model | | 2377 | 12 | 2270 | \Rightarrow | 0.93 | [0.46; 1.88] 92.1% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$ | p = 0 | .83 | | | | | |
| Random effects model | 12 | 2653 | 13 | 2556 | \rightarrow | 0.94 | [0.56; 1.57] 100.0% |
| Prediction interval | | | | | | | [0.52; 1.69] |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$ | | | | | | | |
| Residual heterogeneity: $I^2 = 0$ | %, p = | 0.83 | | | 0.1 0.5 1 2 10 | | |

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.

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.

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

| Study | High- Events | | Low- Events | | | Risk | Ratio | | RR | 9 | 5%-CI | Weight |
|--|-----------------|---------------------|------------------------|------------|-----|------|-------|----|--------------|----------------------|-------------------|----------------|
| Sadeghipour, P Lopes RD | 12 16 | 276 310 | 6 3 | 286 304 | | - | - | | 2.07 5.23 | [0.79; [1.54; | | 58.4% 41.6% |
| Marcos M | 0 | 32 | 0 | 33 | | | | | | | | 0.0% |
| Random effects model Heterogeneity: $I^2 = 28\%$, τ^2 | | 618 s, p = 0 | - 9 0.24 | 623 | 0.1 | 0.5 | 1 2 | 10 | 3.05 | [0.01; 10 | 03.84] | 100.0% |

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

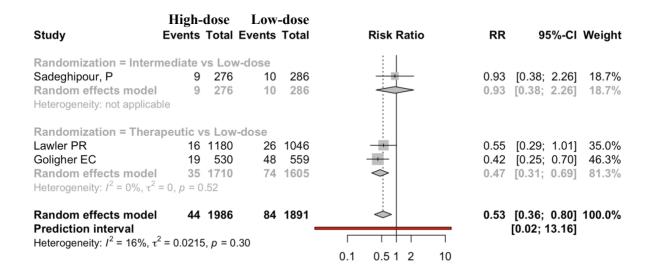
| | High | -dose | Low- | -dose | | | |
|--|--------------|------------------|--------------|------------------|---------------|----------------------|--|
| Study | Events | Total | Events | Total | Risk Ratio | RR | 95%-CI Weight |
| Lopes RD Lemos ACB Sholzberg M | 11 2 2 | 310 10 228 | 18 2 6 | 304 10 237 | | 0.60 1.00 0.35 | [0.29; 1.25] 72.1% [0.17; 5.77] 12.6% [0.07; 1.70] 15.3% |
| Random effects model Prediction interval Heterogeneity: $I^2 = 0\%$, τ^2 | | | 26 | 551 | 0.1 0.51 2 10 | 0.59 | [0.32; 1.10] 100.0% [0.01; 33.24] |

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

| | High-d | lose | Low-c | dose | | | |
|--|----------------------------------|------------------------|------------------|------------------------|------------|-------------------|--|
| Study | Events | Total | Events | Total | Risk Ratio | RR | 95%-CI Weight |
| Lopes RD Lemos ACB Sholzberg M Marcos M | 10 0 2 0 | 310 10 228 32 | 4 0 4 0 | 304 10 237 33 | - | 2.45 0.52 | [0.78; 7.73] 58.3% 0.0% [0.10; 2.81] 41.7% 0.0% |
| Random effects model Heterogeneity: I^2 = 55%, τ | 12 ² = 0.6606, | 580 , p = 0 | .14 | 584 | 1 0.5 1 2 | 1.28 10 | [0.29; 5.75] 100.0% |

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.

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

| | _ | dose Total E | Low- | | | Risk Ratio | RR | 95%-CI | Weight |
|---|--------|-----------------|-------|-------|-----|------------|---------------|---------------|---------|
| Study | CIILS | TOtal L | vents | lotai | | KISK Katio | KK | 93 /0-01 | vveigni |
| Randomization = Intermed | iate | s Low-c | dose | | | | | | |
| Sadeghipour, P | 7 | 276 | 4 | 286 | | - + | – 1.81 | [0.54; 6.13] | 15.1% |
| Random effects model | 7 | 276 | 4 | 286 | | | - 1.81 | [0.54; 6.13] | 15.1% |
| Heterogeneity: not applicable | | | | | | | | | |
| | | | | | | | | | |
| Randomization = Therape | utic v | s Low-d | ose | | | | | | |
| Lawler PR | 22 | 1180 | 9 | 1047 | | - | - 2.17 | [1.00; 4.69] | 37.6% |
| Goligher EC | 20 | 529 | 13 | 562 | | + - | 1.63 | [0.82; 3.25] | 47.3% |
| Random effects model | 42 | 1709 | 22 | 1609 | | | 1.85 | [1.11: 3.10] | 84.9% |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, | p = 0 | .59 | | | | | | | |
| | , | | | | | | | | |
| Random effects model | 49 | 1985 | 26 | 1895 | | | 1.85 | [1.15; 2.96] | 100.0% |
| Prediction interval | | | | | | | | [0.09; 39.65] | |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, | p = 0 | .87 | | | | | | . , | |
| | | | | | 0.1 | 0.5 1 2 | 10 | | |

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.

Summary of findings table

| | | | participants (studies) | evidence (GRADE) | |
|------------------|------------------------|--------------------------|------------------------|--------------------------------|--|
| Venous | PP 0 53 (0 11 to 0 60) | 27 per 1000 fewer events | (8) CUV5 | $\Theta \oplus \oplus \Theta$ | High-dose thromboprophylaxis reduces the |
| thromboembolism | KK 0.55 (0.41 to 0.05) | (17 fewer to 38 more) | 5402 (6) | Moderate ^a | risk of venous thromboembolism |
| Maior blooding | DD 170 (170 to 7 C) | 11 per 1000 more events | 5470 (0) | $\oplus \oplus \oplus \ominus$ | High-dose thromboprophylaxis increaased |
| iviajoi oteeunig | NK 1./8 (1.20 to 2:00) | (3 more to 17 more) | 54/0 (3) | Moderatea | the risk of major bleeding |

^aDowngraded 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 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 |

| | 0.4 1 111 111 1 1 1 |
|----------------------------------|---|
| 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. |