Full versus prophylactic-intermediate doses of anticoagulants in COVID-19: a meta-analysis

by Lorenzo Loffredo, Augusto Di Castelnuovo, Giovanni Alfonso Chiariello, Pasquale Pignatelli, and Francesco Violi

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Full versus prophylactic-intermediate doses of anticoagulants in COVID-19: a meta-analysis.

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Conflicts of interest
All the authors declare that they have no conflicts of interest concerning this paper.

All the data used to support the results of this study are available from the corresponding author upon request.

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Coronavirus disease-19 (COVID-19) is a serious pandemic associated with an elevated risk of venous and arterial thrombosis\(^1\). There is not consensus on the anticoagulant approach to be implemented to reduce the thrombotic risk; thus, most international guidelines recommend standard thromboprophylaxis with use of intermediate doses restricted to high-risk and critically ill patients\(^2\). Therapeutic dosage superiority of anticoagulants in reducing thrombosis in moderately but not severely ill patients or uncertain cost-benefit of full-intermediate anticoagulation versus prophylactic doses were reported by previous meta-analyses\(^3,4\). Therefore, we decided to perform a new, updated meta-analysis of randomized clinical trials comparing the effects of full anticoagulation (FA) versus prophylactic/intermediate anticoagulation (PIA) on death and thrombotic-related events in COVID-19 patients.

**Methods Used:** **ELIGIBILITY CRITERIA.** Types of studies: randomized clinical trial studies that assessed the effect of therapeutic vs prophylactic anticoagulant therapy in COVID-19 hospitalized patients. No language, publication date, or publication status restrictions were imposed. We conducted all analyses according to the intention-to-treat principle. For trials with a factorial design, we based main results on 2-way analyses, that is, all trial participants receiving FA were compared with all those treated with PIA dose. **INFORMATION SOURCES.** The studies were identified by searching electronic databases. This search was applied to Pubmed, ISI Web of Science, SCOPUS and Cochrane database. The last search was run on November 14, 2021. Reference lists of all studies included in the present metanalysis were screened for potential additional eligible studies. **SEARCH.** Two investigators independently searched in the electronic databases combining the following text terms and MeSH terms: "COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "NCOV"[All Fields] OR "2019 NCOV"[All Fields] AND "thrombosis"[MeSH Terms] OR "thrombosis"[All Fields]) AND "anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields]) AND "humans"[MeSH Terms]Studies. We limited our search to human studies. **STUDY SELECTION.** Two authors independently reviewed titles and abstracts generated by search. Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our meta-analysis. Studies not including a control group and animal studies were excluded. Case reports, editorials, commentaries, letters, review articles, guidelines were also excluded from the analysis. We defined the following exclusion criteria: (1) studies that included only the intermediate anticoagulation; (2) studies unrelated to our topic; (3) studies without randomization assignment of the treatment. A flow-chart of the selection studies is reported in Supplementary data (Figure S1). Main analysis We evaluated the effect of FA vs PIA dose in COVID-19 hospitalized patients. Our primary outcome was to compare the effect of these treatments on death and thrombotic events. Our secondary endpoints were the comparison of these treatments on death, arterial and venous thrombotic events, arterial thrombotic events and VTE; the safety endpoint was to evaluate the effect on major bleedings. This metanalysis was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement issued in 2009.
Statistical analysis We allocated the results of each trial as dichotomous frequency data. Risk Ratios (RR) and 95% confidence intervals (CIs) were calculated. Data were pooled and compared with a random-effect model. We calculated the number needed to treat (NNT) and the number needed to harmful (NNH) as the reciprocal of the absolute risk reduction (ARR).

Statistical heterogeneity was calculated by the I². Presence of publication bias was explored using funnel plots of effect size against standard error and Egger’s test. The software Comprehensive Meta Analysis (version 2.2.064, USA, 2011) and R (version 3.1.2, Vienna, 2014) supported the analysis.

Seven studies 5-11 evaluated the effect of FA vs PIA. The relevant parameters of each study is reported in the Table. Antiplatelet drugs were a little bit more frequently used in patients treated with FA (11.9%) versus PIA (10.6%). An heterogeneous definition of the severity of COVID-19 infection was found among the studies. Briefly, we considered as severe patients those: hospitalized at admission in ICU, or with respiratory failure requiring mechanical ventilation or organ support as high flow oxygen, extracorporeal life support, vasopressors, or inotropes. Comparison between subgroups with severe and non-severe disease was pre-specified analysis.

Funnel plots are reported in Supplementary data (Figure 2).

No difference was observed between the rates of death and thrombotic events (as composite outcome) in patients treated with FA (16.5%) versus PIA (19.9%) in 7 studies including 4,734 patients (Figure 1 panel A). Subgroup analysis according to severity showed a lower rate of this composite outcome in patients treated with FA as compared to those treated with PIA in non-severe (RR=0.53, 95%CI: 0.30-0.94), but not in severe patients (Figure 1 panel A).

No difference was observed between the rates of death in patients treated with FA (15.4%) and PIA (14.8%) in 7 studies including 4,741 patients (Figure 1 panel B).

In 7 studies including 4,732 patients a difference was observed between the rates of arterial and venous thrombotic events in patients treated with FA (4.0%) compared to those treated with PIA (7.2%, RR=0.58, 95%CI: 0.45-0.76), both in severe and non-severe patients (Figure 1 panel C).

In six studies (N=4,667 patients) a difference was observed between the rate of venous thrombotic events (VTE) in FA (2.7%) versus PIA patients (5.9%, RR=0.47, 95%CI: 0.35-0.63), both in severe and non-severe patients (Figure 2 panel A).

No significant difference was observed between the rates of arterial thrombotic events in 3 studies including 1,332 patients treated with FA or PIA (Figure 2 panel B).

Six studies, including 4,650 patients, reported major bleeding rates. Major bleeding was observed with an higher rate in FA (2.5%) versus PIA patients (1.4%, Figure 2 panel C).

Number Needed to Treat (NNT) and Number Needed to Harm (NNH) values for major bleedings and several outcomes are reported in supplementary data (Figure 3), in all studies and according to severity.

The study suggests a beneficial effects of FA towards venous thrombosis compared to PIA COVID-19 patients. Even if the risk of major bleeding is higher in FA-treated patients, the overall cost-benefit of treatments is in favor of FA.
It is, so far, unclear whether FA is superior to lower doses of anticoagulants such as PIA on the incidence of death, arterial and venous thrombosis, and major bleeding in COVID-19 patients. The results of the present study show that, in comparison with PIA, FA did not affect the rate of death or arterial thrombosis but reduced the incidence of venous thrombosis whatever is the clinical presentation, i.e. severe or non-severe disease. As expected, the rate of major bleeding was higher in patients on FA. Concomitant treatment with antiplatelet drugs may be an important confounder as we would expect a higher risk of bleeding in patients under full anticoagulation but lack of clinical information on this specific sub-group precludes definite conclusion. The study has implications and limitations. Even if the full anticoagulation did not reduce the risk of death, the positive impact on VTE is of clinical relevance for the management and the potentially harmful long-term effects of VTE; in accordance with this, for VTE and major bleeding the NTT and NNH are 31 and 90 respectively and NTT/NNH 0.34. This finding adds more to the previous meta-analyses as the bleeding risk seems to be lower and the cost-benefit in favor of full anticoagulation in either moderate or severely ill patients. Clinical outcomes were restricted to 30 day- follow-up, thereby it is unclear the impact of several anticoagulant regimens on clinical outcomes, death included, during long-term follow-up.

In conclusion, the results of this meta-analysis suggest the potential usefulness of FA to reduce VTE in COVID-19 patients with either severe or non-severe disease. Further RCTs with large sample size are needed to support this finding.

References

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<th>Study</th>
<th>Definition of disease state at baseline</th>
<th>Disease state at baseline</th>
<th>Primary Endpoints</th>
<th>Male (%)</th>
<th>Age</th>
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<th>Antiplatelets and corticosteroid</th>
<th>Prophylactic / intermediate dose Duration</th>
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<tr>
<td>Action²</td>
<td>Moderate disease was defined by an oxygen saturation &lt;94%, pulmonary infiltrates &gt;50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio &lt;300. Severe disease was defined as respiratory failure, haemodynamic instability, or multiple organ dysfunction. Mild disease includes cases not meeting the criteria for moderate or severe disease.</td>
<td>Severe: (n=311) patients treated with therapeutic doses (Mild: 10%, Moderate: 83%, Severe: 8%).</td>
<td>60</td>
<td>56</td>
<td></td>
<td>rivaroxaban (20 mg once daily) for patients with a stable condition or enoxaparin (1 mg/kg twice daily) for patients with an unstable condition</td>
<td>Antiplatelet: Therapeutic: 25/310 (8.1%) Prophylactic: 30/304 (9.9%)</td>
<td>Standard in-hospital enoxaparin or UFH 30 days</td>
</tr>
<tr>
<td>HEP-COVID⁷</td>
<td>The study included patients with D-dimer criterion greater than 4 times the upper limit of normal or a sepsis-induced coagulopathy score ≥4. The study considered severe patients those hospitalized in ICU and not severe the “Non-ICU stratum”.</td>
<td>Severe: (n=84) and Not Severe: (n=45) patients were treated with therapeutic doses.</td>
<td>53</td>
<td>66</td>
<td></td>
<td>Enoxaparin at a dose of 1 mg/kg s.c. twice daily if CrCl was 30 mL/min/1.73m² or greater or 0.5 mg/kg twice daily if CrCl was 15-29 mL/min/1.73m²</td>
<td>Antiplatelet: Therapeutic: 40/129 (31.0%), Prophylactic: 24/124 (19.4%) Corticosteroid: Therapeutic: 111/127 (87.4%), Prophylactic: 93/123 (75.6)</td>
<td>Heparin regimens could include UFH up to 22 500 IU s.c. (twice or thrice daily); enoxaparin, 30 mg or 40 mg s.c. once or twice daily (weightbased enoxaparin 0.5mg/kg subcutaneously twice daily was permitted); or dalteparin, 2500 IU or 5000 IU s.c. daily 30 days</td>
</tr>
<tr>
<td>RAPID¹</td>
<td>Moderate illness was defined as admission to hospital ward level of care (not to ICU), not already mechanically ventilated, and not imminently requiring mechanical ventilation or critical care. D-dimer levels were required to be above the upper limit of normal with an oxygen saturation ≤93% on room air, or ≥2 times the upper limit of normal irrespective of oxygen saturation.</td>
<td>Not Severe: (n=465)</td>
<td>56</td>
<td>60</td>
<td></td>
<td>Patients allocated to therapeutic heparin received therapeutic doses of LMWH or UFH as used for the treatment of venous thromboembolism.</td>
<td>Antiplatelet: Therapeutic: 24/228 (10.7%), Prophylactic: 29/237 (12.1%) Corticosteroid: Therapeutic: 161 (70.6 %), Prophylactic: 162 (68.4 %)</td>
<td>Patients allocated to prophylactic heparin received dose capped prophylactic s.c. heparin (LMWH or UFH) adjusted for body mass index and creatinine clearance. 28 days</td>
</tr>
<tr>
<td>ATTACC, ACTIV-4a, and REMAP-CAP Investigators⁹</td>
<td>Moderate disease was defined as hospitalization for Covid-19 without the need for ICU-level care. ICU-level care was defined as the use of respiratory or cardiovascular organ support in an ICU.</td>
<td>Not Severe: (n=2231)</td>
<td>59</td>
<td>59</td>
<td></td>
<td>Therapeutic-dose anticoagulation with UFH or LMWH</td>
<td>Antiplatelet: Therapeutic: 148/1140 (13.0%), Prophylactic: 111/1013 (11.0%) Corticosteroid: Therapeutic: 479/701 (66.0 %), Prophylactic: 415/656 (63.3)</td>
<td>Usual-care pharmacologic thromboprophylaxis 21 days</td>
</tr>
<tr>
<td>ATTACC, ACTIV-4a, and REMAP-CAP Investigators⁹</td>
<td>Severe Covid-19 was defined as Covid-19 that led to receipt of ICU-level respiratory or cardiovascular organ support in an ICU.</td>
<td>Severe: (n=1103)</td>
<td>70</td>
<td>61</td>
<td></td>
<td>Therapeutic-dose anticoagulation with UFH or LMWH</td>
<td>Antiplatelet: Therapeutic: 37/485 (7.6), Prophylactic: 38/494 (7.7) Corticosteroid: Therapeutic: 426/522 (81.6), Prophylactic: 458/555 (82.5)</td>
<td>Usual-care pharmacologic thromboprophylaxis 21 days</td>
</tr>
<tr>
<td>HESA-COVID⁸</td>
<td>Severe clinical presentation with respiratory failure requiring mechanical ventilation, D-dimer levels greater than 1000 μg/L.</td>
<td>Severe: (n=29)</td>
<td>80</td>
<td>56</td>
<td></td>
<td>Enoxaparin s.c. with the dose according to age and adjusted daily by the creatinine clearance</td>
<td>Antiplatelet: Therapeutic: 0/10 (0%), Prophylactic: 0/10 (0%). Corticosteroid: Therapeutic: 7/70 (70), Prophylactic: 7/70 (70)</td>
<td>The standard thromboprophylaxis group was allocated to receive s.c., UFH at a dose of 5000 IU TID (if weight&lt;120 kg) and 7500 IU TID (if weight&gt;120 kg) or enoxaparin at a dose of 40 mg OD (if weight&lt;120 kg) and 40 mg BD (if weight&gt;120 Kg). 14 days</td>
</tr>
<tr>
<td>BEMICOP¹¹</td>
<td>positive COVID-19 diagnosis CURB≥2, baseline blood oxygen saturation ≥90%</td>
<td>Not severe: (n=65)</td>
<td>62</td>
<td>63</td>
<td></td>
<td>Bamlanivimab 115 IU/kg once daily adjusted for body weight.</td>
<td>Antiplatelet drug was an exclusion criterium Corticosteroids: Therapeutic: 30/33 (90 %) Prophylactic: 32/32 (100)</td>
<td>Bamlanivimab 3500 IU once daily 10 days</td>
</tr>
</tbody>
</table>
Table
Characteristics of the studies
* International Society on Thrombosis and Haemostasis (ISTH) criteria: fatal bleeding; symptomatic bleeding in a critical area or organ; hemoglobin level <2 g/dL or more; bleeding leading to transfusion of 2 or more units of whole blood or red cells.
** TIMI criteria: defined as: - Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI) - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit - Fatal bleeding.

Legend

Figure 1
Forrest Plots of death and thrombotic events.
Forest plots for death and thrombotic events according to the subgroups for FA and PIA doses (Panel A).
Forest plots for death according to the subgroups for FA and PIA doses (Panel B).
Forest plots for arterial and venous and thrombotic events according to the subgroups for FA and PIA doses (Panel C).

Figure 2
Forrest Plots of thrombotic events and bleeding.
Forest plots for venous thrombotic events according to the subgroups for FA and PIA doses (Panel A).
Forest plots for arterial thrombotic events (Panel B).
Forest plots for major bleeding events according to the subgroups for FA and PIA doses (Panel C).