Anticoagulation Literature Review: COVID-19 Clinical Advisory Group Update
February 2022

Background:
- Coronavirus disease 2019 (COVID-19)–related critical illness and acute illness are associated with a risk of venous thromboembolism (VTE).
- Recommendations to date have been based on very low certainty evidence, underscoring the need for high-quality, randomized controlled trials comparing different intensities of anticoagulation.

Data Summary:
- Randomized Controlled Trials1-9
  - **ICU Patients**
    - Findings from a conglomerate of three open-label, pragmatic, adaptive, multiplatform, multicenter, randomized controlled trials (REMAP-CAP, ACTIV-4a, and ATTACC; (n=1098)) evaluating therapeutic anticoagulation with low or intermediate-dose thromboprophylaxis reported no differences in the primary endpoint (organ support-free days) or mortality for patients with severe illness (ICU care). There was a nonsignificant, small trend towards more bleeding in the full anticoagulation group (3.8% vs 2.3%) and lower risk of major thrombotic events (6.4% vs 10.4%).
    - Similarly, results from the INSPIRATION randomized clinical trial (and Perepu et al.) do not support the routine empirical use of intermediate-dose prophylactic anticoagulation in ICU patients with severe COVID-19.
  - **Non-ICU Patients**
    - Published data from the mpRCT conglomerate—ATTACC, ACTIV, REMAP-CAP, suggest full dose anticoagulation in moderately ill hospitalized patients with COVID-19 may improve organ support free days and survival. Additionally, results from the HEP-COVID trial (n=252) found a significant 13.2% absolute reduction in the composite of arterial and venous thrombosis and all-cause mortality in non-ICU, moderately ill patients (67.2% of the trial population) treated with therapeutic LMWH.
    - These findings were not supported by two open-label, pragmatic RCTs (ACTION and RAPID) which reported no significant difference in composite efficacy outcomes and potentially an increased risk of major bleeding (ACTION).
    - Intermediate dose enoxaparin did not improve the general clinical outcomes of the patients compared to standard dose during the X-COVID-19 trial.
- Systematic Review and Meta-Analyses7, 10-15
  - Meta-analysis of RAPID and mpRCT did not provide conclusive evidence of mortality benefit with therapeutic anticoagulation in moderately ill patients with COVID-19 but may be associated with improvement in organ support-free days and ventilator free-days alive.
  - Pooled results of 7 RCTs in a recent meta-analysis found no difference in mortality for escalated doses of anticoagulation (intermediate or therapeutic) compared to standard prophylactic dosing. In subgroup analyses, there was also no difference in mortality for those treated in the ICU or for non-ICU hospitalized patients. Major bleeding was increased in the escalated group but remained low at 2.4%.
  - Results of a second meta-analysis of 8 RCTs indicate that moderately affected COVID-19 patients may benefit from therapeutic-dose anticoagulation compared to standard prophylaxis based on the results of the RAPID trial in 465 patients. However, little or no effect was shown for in-hospital mortality based on the large ATTACC, ACTIV-4a, REMAP-CAP platform trial with 2226 participants. As such, certainty of evidence is still low for survival benefit in hospitalized COVID-19 patients at the cost of increased bleeding independent of disease severity.
**Data Summary (Continued):**

**Study**

<table>
<thead>
<tr>
<th>Study Code</th>
<th>Sample Size (Estimated)</th>
<th>Study Design/Status</th>
<th>Inclusion Criteria</th>
<th>Treatment vs Comparator</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04086662 (ANTICOVID)</td>
<td>353</td>
<td>Phase 2, randomized, open-label, parallel assignment</td>
<td>Recruiting Hospitalized adults ≥ 18 years (up to 85) with severe COVID admitted ≤ 72 hours (WHO &lt; 5 or &gt; 72 hours from admission to ICU (WHO &lt; 6) (France)</td>
<td>Tinzaparín, low dose prophylactic anticoagulation</td>
<td>All-cause mortality</td>
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<tr>
<td>NCT04406389 (IMPACT)</td>
<td>186</td>
<td>Phase 4, randomized, open-label, parallel assignment</td>
<td>Recruiting Hospitalized COVID-19 adults ≥ 18 years ICU (or non-ICU) within 72 hours of fever, J2 Sat ≤ 94, D-dimer ≥ 1.0 mcg/mL, Platelets &gt; 100,000 mcg/L, CRP &gt; 150 mcg/L.</td>
<td>Prophylactic enoxaparin</td>
<td>30-day mortality</td>
</tr>
<tr>
<td>NCT04512079 (FREEDOM COVID)</td>
<td>3600</td>
<td>Phase 4, randomized, open-label, parallel assignment</td>
<td>Recruiting Hospitalized COVID+ adults ≥ 18 years within 72 hours w/ fever, O2 Sat ≤ 94, D-dimer ≥ 1.0 mcg/mL, Platelets &gt; 100,000 mcg/L, ANC &lt; 1500 cells/m3 (International)</td>
<td>Prophylactic enoxaparin</td>
<td>Time to first event</td>
</tr>
<tr>
<td>NCT04416048 (COVID-PREVENT)</td>
<td>400</td>
<td>Phase 2, randomized, open-label, parallel assignment</td>
<td>Recruiting Hospitalized adults ≥ 18 years with moderate-to-severe COVID (non-mechanically ventilated) within last 14 days and D-dimer &gt; 1.5 ULN or evidence of cardiac injury (Germany)</td>
<td>Therapeutic rivaroxaban for at least 7 days or until hospital discharge</td>
<td>Composite endpoint of venous thromboembolism, arterial thromboembolism</td>
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<tr>
<td>NCT04542406 (HERO-19)</td>
<td>172</td>
<td>Phase 3, randomized, double-blind, parallel assignment</td>
<td>Recruiting Hospitalized adults ≥ 18 years ICU and non-ICU and COVID diagnosis within 10 days with troponin ≥ULN and/or D-Dimer ≥ 0.5 mg/L (Germany)</td>
<td>Therapeutic edoxaban and/or high dose LMWH or low dose LMWH or placebo</td>
<td>Composite endpoint of all-cause mortality, venous thromboembolism, arterial thromboembolism</td>
</tr>
<tr>
<td>NCT04730850 (PROTHROMCovid)</td>
<td>600</td>
<td>Phase 3, randomized, open-label, parallel assignment</td>
<td>Recruiting Hospitalized COVID+ adults ≥ 18 years (wt 50-100kg) with at least one of the following: O2 Sat &lt; 94%, need for oxygen or PaO2/FiO2 &lt; 300 mmHg, D-Dimer &gt; 100 mcg/L, PCR &gt; 150 mg/L, IL-6 &gt; 40 pg/mL (Spain)</td>
<td>Tinzaparín, low dose prophylactic anticoagulation</td>
<td>Reduction of suspicion of systemic thrombotic symptomatic events</td>
</tr>
<tr>
<td>NCT04360824</td>
<td>170</td>
<td>Phase 4, randomized, open-label, parallel assignment</td>
<td>Recruiting Hospitalized COVID+ adults ≥ 18 years and Modified ISTH Overt DIC score ≥3 (United States)</td>
<td>Enoxaparin intermediate dose vs standard prophylaxis</td>
<td>30-day mortality</td>
</tr>
<tr>
<td>NCT04745339 (APELLO)</td>
<td>1000</td>
<td>Phase 4, randomized, quadruple-blind, parallel assignment</td>
<td>Recruiting Outpatient with symptomatic COVID-19 and D-Dimer ≥ 2x ULN or CRP ≥ 10 mg/L, and at least two additional risk factors (Brazil)</td>
<td>Apixaban 2.5 mg BID for 30 days</td>
<td>Number of days alive and out of hospital or emergency department</td>
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<td>NCT04560714 (ACTIV-A4A)</td>
<td>3000</td>
<td>Phase 4, randomized, adaptive, open-label, sequential assignment</td>
<td>Recruiting Hospitalized COVID+ adults ≥ 18 years within 72 hours with moderate-to-severe illness (United States)</td>
<td>Therapeutic dose heparins (stopped in severe patients 12/2021; stopped in moderate patients 6/2021)</td>
<td>21 Day Organ Support Free Days</td>
</tr>
<tr>
<td>NCT04377997</td>
<td>300</td>
<td>Phase 2, randomized, open-label, parallel assignment</td>
<td>Not Yet Recruiting Hospitalized COVID+ adults ≥ 18 years with moderate illness and fibrinogen &gt; 100, PLT &gt;50, D-Dimer &gt; 1500 ng/mL (Mass General)</td>
<td>Therapeutic enoxaparin or UFH</td>
<td>Composite efficacy end point of death, cardiac arrest, symptomatic DVT, PE, arterial thromboembolism, myocardial infarction, or hemodynamic shock</td>
</tr>
<tr>
<td>NCT04341775 (CORMIMMUCOAG)</td>
<td>808</td>
<td>Phase 2, randomized, open-label, parallel assignment</td>
<td>Not Yet Recruiting Hospitalized COVID+ non-ICU adults ≥ 18 years with mild-to-severe pneumonia within 14 days of onset with need for oxygen but not NIV or HFNC; patients with respiratory failure and requiring mechanical ventilation with WHO ≥ 6 (France)</td>
<td>Therapeutic tinzaparín or UFH</td>
<td>Survival without ventilation</td>
</tr>
<tr>
<td>NCT04342048 (COVID-HEP)</td>
<td>160</td>
<td>Phase 3, randomized, single-blind, parallel assignment</td>
<td>Terminated (low recruitment)</td>
<td>Therapeutic enoxaparin or UFH</td>
<td>Composite outcome of arterial or venous thrombosis, disseminated intravascular coagulation and all-cause mortality</td>
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</table>
Data Summary (Continued):

- **Guideline Recommendations:**
  - **NIH (January 2022):** Hospitalized nonpregnant adults with COVID-19 who have a D-dimer above the upper limit of normal (ULN), require low-flow oxygen, have no increased bleeding risk, and are not receiving ICU level of care should receive therapeutic-dose heparin (CIIa). Hospitalized ICU nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation unless a contraindication exists (AI).
    - *In patients without a VTE who are started on therapeutic-dose heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first.*
    - *For patients who start on therapeutic-dose heparin while on low-flow oxygen due to COVID-19 and then transfer to the intensive care unit (ICU), the Panel recommends switching from therapeutic to prophylactic-dose heparin unless a VTE is confirmed (BIII).*
  - For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated (BIII). LMWH is preferred over unfractionated heparin.
    - *Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 in the absence of a known VTE.*
  - **American Society of Hematology (December 2021):** ASH guidelines currently suggest using therapeutic-intensity over prophylactic-intensity anticoagulation for non-ICU patients with COVID-19–related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation, very low certainty).
    - *Patients with COVID-19–related acute illness are defined as those with clinical features that would typically result in admission to a medicine inpatient ward without requirement for advanced clinical support. Examples include patients with dyspnea or mild to moderate hypoxia.*
  - Other societal guidelines (i.e. Anticoagulation Forum, ISTH, CHEST, SCCM, WHO) favor the use of standard prophylactic anticoagulation for most hospitalized patients with COVID-19. However, updated guidance statements are not available within the last 12 months.

Recommendations:

- Given variable interventions, primary outcomes measures, and different methods of analyses of recent randomized controlled trials, it remains uncertain if higher intensity anticoagulation offers net benefit over standard thromboprophylaxis in patients hospitalized for COVID-19, particularly in moderately ill patients. Available evidence is monitored regularly, and guidance is updated as more information becomes available.
- Based on the totality of data to date, updated guidelines and guidance documents favor the use of standard prophylactic anticoagulation for most hospitalized patients with COVID-19. Use of therapeutic anticoagulation for the purpose of thromboembolism prophylaxis should be done selectively in moderately ill patients with a determination of net clinical benefit.
- For hospitalized adults with COVID-19 admitted within the last 72 hours and without an increased bleeding risk, therapeutic anticoagulation in the absence of objectively confirmed VTE can be considered for patients who require low-flow oxygen and have a D-dimer above upper limit of normal (ULN).
  - For pregnant patients, the following additional criteria must be met:
    - Not at high risk for emergent delivery or heavy bleeding
    - D-dimer > 2 x ULN
    - Shared decision making and individual risk assessment always recommended, MFM colleagues available for consultation PRN
  - Exclusion: Patients receiving ICU level care, hospital discharge anticipated within 72 hours, PLT < 50, Hemoglobin < 8 g/dL, need for dual antiplatelet therapy, known bleeding within the last 30 days, known history of bleeding disorder, or an inherited or active acquired bleeding disorder.
  - In patients without a VTE who are started on therapeutic-dose anticoagulation, treatment should continue for 14 days or until hospital discharge, whichever comes first.
  - For patients who start on therapeutic-dose anticoagulation while on low-flow oxygen due to COVID-19 and then transfer to the intensive care unit (ICU), therapeutic anticoagulation should be switched to prophylactic-dose heparin unless a VTE is highly suspected or confirmed.
- Clinicians should continue to weigh the potential benefit and harms based on the most up-to-date available evidence in caring for their patients.
### X-COVID-19, Dec 2021

**LOE 1b, n = 253**

An open-label, multicenter, prospective, active control, parallel-arm randomized trial in hospitalized patients with COVID-19 admitted to medical wards across at 9 centers in Italy between April 30 2020 and April 25 2021.

**1:1 randomization to enoxaparin 40 mg SUBQ once daily or enoxaparin 40 mg SUBQ BID continued until discharge**

**Inclusion:**
- Adults aged > 18 years with PCR-confirmed SARS-CoV-2 infection

**Exclusion:**
- Directly admitted to ICU
- Estimated creatinine clearance <15 ml/min/1.73 m² (CKD-EPI formula)
- Anticoagulant treatment for prior indications
- Treatment with heparin at higher doses than recommended for thromboprophylaxis
- Bleeding or at high bleeding risk (according to the judgement of the most responsible physician)
- Involved in competitive RCT exploring antithrombotic treatments or had any other condition that could either expose them at risk because of participation in the RCT or negatively affect their ability to participate in the RCT

**Primary outcome:**
- Higher dose enoxaparin was associated with lower absolute risk of incidence of VTE compared to 40 mg once daily (0 vs 6, ARR 6.5; [95% CI: 1.5–11.6])

**Secondary outcome:**
- Incidence of overall death, VTE, use of mechanical ventilation, stroke, acute myocardial infarction and admission to ICU was similar between groups (13% vs 9.9%, ARR 3.1; [95% CI: -6.0-12.4])
- A lower risk of death was observed in the enoxaparin once daily group compared to 40 mg BID (1.1% vs 5.5%; ARR -4.4; [95% CI: -9.5–0.7])
- No statistically significant differences were observed in other secondary outcomes

**Adverse events:**
- There were 2 ISTH major bleeding events (type 5 and 3a BARC); 1 in the enoxaparin once daily group (1.1%) and a fatal bleeding event in the enoxaparin BID group (1.1%)
- 1 ISTH minor bleeding (BARC 2) event occurred in the enoxaparin BID group
- No cases of HIT were reported

**Patient selection:**
- Median age 59, male (62.8%), median BMI 25 [23-28], median D-dimer 0.35 mcg/ml [0.19-0.71]
- The two study groups were well-balanced for baseline clinical and laboratory characteristics
- Median duration of anticoagulation was slightly higher in the 40 mg BID enoxaparin group compared to prophylactic regimen (9 vs. 7 days)
- Concomitant pharmacological treatments and respiratory support were comparable

**Adverse events:**
- No statistically significant difference

**Conclusions:**
- Standard dose enoxaparin was associated with higher incidence of VTE but lower risk of death compared to intermediate dose (40 mg BID).
- In general, high doses of anticoagulants did not improve the general clinical outcomes of the patients.

**Limitations:**
- Underpowered for primary endpoint compared to the originally planned sample size.
- The study was interrupted prematurely due to slow recruitment.
- Randomization during the COVID-19 pandemic has been a challenge. Among the 3550 provisionally eligible patients, clinicians excluded 3364, in many cases due to the lack of personal equipoise.
- Minority of enrolled patients failed to undergo all the planned systematic CUS evaluations; thus some asymptomatic DVT events could have been missed.
- The median duration of anticoagulation was slightly higher in the 40 mg BID enoxaparin group compared to prophylactic regimen (9 vs. 7 days). The fact that it did not reach statistical significance may be due to low statistical power.

### HEP-COVID, Oct 2021

**LOE 1b, n = 253**

A randomized clinical trial recruited hospitalized adult patients with COVID-19 with D-dimer levels more than 4 times the upper limit of normal or sepsis-induced coagulopathy score of 4 or greater from May 8, 2020 through May 14, 2021 at 12 academic centers in the US.

**Patients were randomized to institutional standard prophylactic or intermediate-dose LMWH (n=124) or unfractionated heparin vs therapeutic-dose enoxaparin (n=129).** Patients were stratified at the time of randomization based on intensive care unit (ICU) or non-ICU status.

**Inclusion:**
- Adults aged > 18 years with PCR-confirmed SARS-CoV-2 infection

**Exclusion:**
- Directly admitted to ICU
- Estimated creatinine clearance <15 ml/min/1.73 m² (CKD-EPI formula)
- Anticoagulant treatment for prior indications
- Treatment with heparin at higher doses than recommended for thromboprophylaxis
- Bleeding or at high bleeding risk (according to the judgement of the most responsible physician)
- Involved in competitive RCT exploring antithrombotic treatments or had any other condition that could either expose them at risk because of participation in the RCT or negatively affect their ability to participate in the RCT

**Primary outcome:**
- Compared with standard-dose heparins, therapeutic-dose LMWH reduced the incidence of the VTE, ATE, or death within 28-32 days among non-ICU patients (36.1% vs 16.7%; RR 0.46; [95% CI: 0.27-0.81]; p = 0.004) but not ICU patients (55.3% vs 51.1%; RR 0.92; [95% CI: 0.62-1.39]; p = 0.71)
- There was no significant difference in major bleeding between groups, although there were numerically more major bleeds among ICU patients treated with therapeutic-dose compared with the standard-dose group (4 (8.9%) vs 0; RR 7.62; [95% CI: 0.42-137.03]; p = 0.12)

**Secondary outcome:**
- Therapeutic-dose LMWH reduced the incidence of VTE, ATE, or death at day 14 (36.3% vs 23.3%; RR 0.64; [95% CI: 0.43-0.95]; p = 0.02)
- There were no significant differences in other secondary outcomes between groups

**Adverse events:**
- No statistically significant difference

**Conclusions:**
- Therapeutic-dose LMWH reduced the composite of thromboembolism and death compared with standard heparin thromboprophylaxis without increased major bleeding among non-ICU hospitalized patients with COVID-19 with elevated D-dimer levels > 4x ULN.
- The treatment effect was not seen in ICU patients.

**Limitations:**
- Small sample size.
- Although both investigators and patients were blinded to study drug regimen, other
### Study Design

- **Hospitalized nonpregnant adults** 18 years or older with COVID-19 diagnosed by nasal swab or serologic testing AND
- **Required** supplemental oxygen per investigator judgment
- **Plasma** D-dimer level greater than 4 times the upper limit of normal based on local laboratory criteria OR sepsis-induced coagulopathy score of 4 or greater

### Exclusion:
- Physician-determined need for full-dose anticoagulation or dual antiplatelet therapy
- Bleeding within the past month
- Active gastrointestinal or intracranial cancer
- Bronchiectasis or pulmonary cavitation
- Hepatic dysfunction with baseline INR > 1.5
- Creatinine clearance (CrCl) < 15 mL/min
- Platelet < 25,000 mcg/L
- History of HIT within 100 days
- Hypersensitivity/intolerance to study drug or components

### Results

<table>
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<tr>
<th>Study</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Patients</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>ACTIV-4b, Oct 2021†</td>
<td>n = 657</td>
<td>Aug 5, 2021</td>
<td>n = 657</td>
<td>Aug 5, 2021</td>
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</table>

Participants were randomized centrally in a 1:1:1:1 ratio to receive aspirin (81 mg once daily n=164), prophylactic-dose apixaban (2.5 mg twice daily; n=165), apixaban at therapeutic dose (5 mg twice daily; n=164), or matching placebo (n=164) for 45 days, with a 30-day safety follow-up evaluation

### Inclusion:
- Ambulatory patients between the ages of 40 and 80 years with newly diagnosed symptomatic SARS-CoV-2 infection with positive polymerase chain reaction or antigen test results.
- PLT > 100,000/mm3
- Estimated glomerular filtration rate greater than 30 mL/min/1.73 m2

### Exclusion:
- Previously hospitalized for COVID-19
- Acute leukemia
- Recent major bleeding

### Primary outcome: No statistically significant difference
- No difference in composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause were observed between groups
  - Aspirin, 0.0% ([95% CI: 0.0%-2.6%])
  - Prophylactic apixaban, 0.7% ([95% CI: 0.1%-4.1%])
  - Therapeutic apixaban, 1.4% ([95% CI: 0.4%-5.0%])
  - Placebo, 0.0% ([95% CI: 0.0%-2.8%])

### Secondary outcome: No statistically significant difference
- No significant difference in episodes of myocardial infarction, stroke, or other arterial thromboembolism
- One venous thromboembolism occurred in the aspirin group (0.7%)

### Conclusions

- Among symptomatic clinically stable outpatients with COVID-19, treatment with aspirin or apixaban did not reduce the rate of composite all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization compared with placebo.
- The study was terminated after enrollment of 9% of participants because of an event rate lower than anticipated.

### Limitations:
- Given the time frame of the trial, it is unlikely that many participants were infected with COVID-19 variants, such as the delta variant, that may confer greater clinical severity.
- Very few trial participants had been vaccinated prior to randomization, an issue that could limit generalizability.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEREP, Sep 2021*</td>
<td>A multi-center, open-label, randomized controlled trial comparing standard prophylactic dose versus intermediate dose enoxaparin in adults who were hospitalized with COVID-19 and admitted to an ICU and/or had laboratory evidence of coagulopathy. The trial was conducted at three centers in the United States from April 2020 to January 2021.</td>
<td><strong>Primary outcome: No statistically significant difference</strong>  - No difference in all-cause 30-day mortality were observed between standard prophylaxis and intermediate dosing groups (21% vs 15%; OR 0.66; [95% CI 0.30–1.45]; p=0.31)  <strong>Secondary outcome: No statistically significant difference</strong>  - No difference in arterial or venous thrombosis occurred between groups (9% vs 13%)  - Major bleeding occurred in 2% of patients in each arm  - Minor bleeding occurred in 7% of patients in each arm Patient selection:  - Median age 54 years, women (59.1%), self-identified as Black (12.7%), Hispanic (28.1%), median BMI 30.1, DM (18.3%), history of smoking (19.9%), HTN (35.3%).  - Baseline characteristics were balanced among treatment groups in all randomized participants and among those who initiated treatment.</td>
<td>Use of outpatient interventions such as monoclonal antibody treatment which may further reduce the primary trial event rate was low in this trial.  The median time from diagnosis to randomization was 7 days, so the study findings cannot address the potential efficacy of more immediate intervention.</td>
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<tr>
<td>REMAP-CAP, ACTIV-4a, ATTACC, Aug 2021*</td>
<td>Conglomerate of 3 international, multicenter, open-label, adaptive, multi-platform, randomized controlled trials of 1098 hospitalized patients with severe confirmed COVID-19 (defined as ICU level care or critically ill) between April 2020 and December 2020. 1:1 Randomization (ACTIV-4a) or response-adaptive randomization (REMAP-CAP and ATTACC) to therapeutic anticoagulation</td>
<td><strong>Primary outcome: No statistically significant difference</strong>  - No difference in median organ support free days (therapeutic 3 [-1.16] vs. usual care 5 [-1.16]; aOR 0.83 [95% CI: 0.67-1.03])  - Probability of futility 99.9% and inferiority 95.0%  - 90-day survival (62.7% vs 64.5%; aOR 0.84 [95% CI:0.64-1.11]). Probability of inferiority 89.2%  <strong>Secondary outcome: No statistically significant difference</strong>  - Numerically fewer major thrombotic events observed for those assigned anticoagulation (6.4% vs 10.4%) but no statistically significant difference in</td>
<td>In hospitalized adults with severe COVID-19, intermediate dose enoxaparin did not prevent death or thrombosis at 30 days compared to standard prophylaxis.  Limitations:  - The trial design was based on data available in early 2020 that suggested a mortality of up to 40% in hospitalized patients with severe COVID-19 who were treated with standard prophylactic dose LMWH. Studies performed later in the pandemic suggested a lower in-hospital mortality of 15 to 20%.  - Cannot be extrapolated to all patients hospitalized with COVID-19, because more than 85% of screened patients did not meet the eligibility criteria.  - Both ICU and non-ICU patients were eligible, so results should not be compared directly to other trials limited only to critically ill ICU patients.  - Protocols for dose adjustment for weight were not standardized.  - Not designed to examine outcomes beyond 30 days.</td>
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<tr>
<td>Study</td>
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<td>(n=534) or usual care pharmacological thromboprophylaxis (n=564) according to local site protocols for up to 14 days or recovery</td>
<td>major thrombotic events or death through day 28 or hospital discharge between groups (40.1% vs 41.1%; aOR 1.04 [95% CI: 0.79-1.35])</td>
<td>Whether intermediate dose is superior to standard low-dose prophylaxis in critically ill patients also remains uncertain, but results from INSPIRATION trial suggest no benefit.</td>
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<td>Adverse events: No statistically significant difference</td>
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<td></td>
<td>No significant difference in major bleeding events (3.8% vs 2.3%)</td>
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<td>Patient selection:</td>
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<td>Limitations:</td>
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<td>Open-label, pragmatic design.</td>
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<td>Inclusion:</td>
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<td>Significant overlap between regimens used in the two groups- eight different interventions used (not equivalent to each other), including combination aspirin.</td>
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<td>Adults ≥18 years requiring hospital admission to the ICU within &lt;48 hours (REMAP-CAP) or admission to the hospital within &lt;72 hours (ACTIV-4a, ATTACC)</td>
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<td>Control group was mostly split between low-dose and intermediate-dose anticoagulation.</td>
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<tr>
<td>Exclusion:</td>
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<td>However, only 78% of patients in the therapeutic group received full therapeutic dose anticoagulation (8.3% subtherapeutic dosing, 3.4% low-dose, 8.3% intermediate dose).</td>
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<td>Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization</td>
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<td>Selection of patients may not benefit from therapeutic anticoagulation (low D-dimer).</td>
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<td>Patients for whom the intent is to not use pharmacologic thromboprophylaxis</td>
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<td>Active bleeding Risk factors for bleeding, including: intracranial surgery or stroke within 3 months; history of intracerebral arteriovenous malformation; cerebral aneurysm or mass lesions of the central nervous system; intracranial malignancy, history of intracranial bleeding, history of bleeding diatheses (e.g., hemophilia), history of gastrointestinal bleeding within previous 3 months, thrombosis within the previous 7 days, presence of an epidural or spinal catheter, recent major surgery 200mmHg, dBP &gt;120 mmHg), other physician-perceived contraindications to anticoagulation</td>
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<td>Platelet count &lt;50, INR &gt; 2.0, or baseline aPTT &gt;50</td>
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<td>Hemoglobin &lt; 8 g/dL</td>
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<td>Acute or subacute bacterial endocarditis</td>
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<tr>
<td>History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity</td>
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<tr>
<td>Current use of dual antiplatelet therapy</td>
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<tr>
<td>Patients with an independent indication for therapeutic anticoagulation</td>
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<tr>
<td>Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention</td>
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<tr>
<td>Anticipated transfer to another hospital that is not a study site within 72 hours</td>
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<tr>
<td>Enrollment in other trials related to anticoagulation or antplatelet therapy</td>
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<tr>
<td>Conglomerate of 3 international, multi-platform, RCTs of 2219 hospitalized patients who were NOT critically ill with confirmed COVID-19 between April 2020 and January 2021</td>
<td>Tinzaparin 8000 units BID for BMI ≥40</td>
<td>Therapeutic anticoagulation in noncritically hospitalized adults was associated with increased median organ support free days, improved survival without organ support at 28 days, and fewer thrombotic events.</td>
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</tr>
<tr>
<td>ICU-level care was defined as the use of respiratory or cardiovascular organ support (oxygen delivered by high-flow nasal cannula, noninvasive or invasive mechanical ventilation, or the use of vasopressors or inotropes) in an ICU.</td>
<td></td>
<td>No difference in survival until hospital discharge,</td>
<td></td>
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</table>
Patients who were admitted to an ICU but without receiving qualifying organ support were considered to be moderately ill. Exclusion:
- If 72 hours had lapsed since hospital admission (ATTACC or ACTIV-4a) or 14 days had lapsed (REMAP-CAP)
- Hospital discharge expected within 72 hours
- Clinical indication for therapeutic anticoagulation
- High risk of bleeding
- Receipt of dual antiplatelet therapy
- Known heparin allergy including HIT
- Imminent death

**Study**
- Sholzberg (RAPID), Study designed to dose nomogram UFH or standard prophylaxis [dalteparin, enoxaparin, tinzaparin] or high
  dose UFH or standard prophylaxis
- Randomized controlled trial among 465 moderately ill patients between May 2020 and April 2021
- Randomized to therapeutic LMWH [dalteparin, enoxaparin, tinzaparin, fondaparinux] or UFH
- Administration of LMWH, UFH or fondaparinux at thromboprophylactic doses for acutely ill hospitalized medical patients, in the absence of contraindication, is generally considered standard care
- Study treatment was started within 24 hours after randomization, and continued until the first of hospital discharge, day 28, study withdrawal or death. If a participant was admitted to ICU, continuation of the allocated treatment was recommended

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Primary outcome: No statistically significant difference</strong></td>
<td>Therapeutic anticoagulation was associated with significantly fewer thrombotic event or in-hospital death (8.0% vs 9.9%; aOR 0.72; [95% CI: 0.53-0.98]) without significant increase in major bleeding (1.9% vs 0.9%; aOR 1.80; [95% CI: 0.90-3.74])</td>
</tr>
<tr>
<td><strong>Adverse events:</strong></td>
<td>Fatal bleeding occurred in 3 patients in the anticoagulation group and in 1 patient in the thromboprophylaxis group</td>
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<td>There were no episodes of intracranial bleeding or confirmed HIT</td>
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</table>

**Patient selection:**
- Mean age 59; Further stratified by D-Dimer level: ≥2 x ULN, <2 ULN, unknown
- Patients in the high and unknown d-dimer cohorts were generally older and had a higher prevalence of coexisting illnesses than those in low d-dimer cohort
- Mean BMI 30, most patients had a pre-existing condition (DM, HTN, chronic respiratory disease most common), and required low flow nasal cannula or face mask (66%), or no respiratory support (13%)
- Concomitant baseline therapies included antiplatelet agents (in 12% of the patients), glucocorticoids (62%), and remdesivir (36%)

**Meta-analysis of RAPID and mpRCT:**
- No significant difference in composite of all-cause mortality or any mechanical ventilation (10.1% vs 16.0%; OR 0.59; [95% CI: 0.34-1.02])
- No significant difference was observed in any secondary outcome including death or ICU admission, ventilator free days, hospital-free days alive, ICU-free days alive, renal replacement therapy, thrombotic events
- Safety outcome: No statistically significant difference
- No significant difference in major bleeding observed (0.9% vs 1.7%; OR 0.52; [95% CI: 0.09-2.85])
- There were no fatal bleeding events and there were no cases of intracranial hemorrhage
- In moderately ill patients with COVID-19 and elevated D-dimer levels, therapeutic anticoagulation did not significantly impact primary or secondary clinical efficacy or safety outcomes
- Authors report odds of all-cause death were lower in the therapeutic group compared to those treated with prophylactic dose (1.8% vs 7.6%; OR 0.22; [95% CI: 0.07-0.65])
- Meta-analysis of RAPID and mpRCT of therapeutic anticoagulation in moderately patients with COVID-19 did not provide conclusive evidence for a reduction in mortality but may improve organ support-free days and ventilator free-days alive.

**Conclusions**
- No significant difference in composite of all-cause mortality or any mechanical ventilation, or death up to 28 days were observed in patients treated with therapeutic full dose heparin compared to low dose heparin (16.2% vs 21.9%; OR 0.69; [95% CI: 0.43-1.10]; p=0.12)
- Secondary outcome: No statistically significant difference
- No significant difference in composite of all-cause mortality or any mechanical ventilation (10.1% vs 16.0%; OR 0.59; [95% CI: 0.34-1.02])
- Safety outcome: No statistically significant difference
- No significant difference in major bleeding observed (0.9% vs 1.7%; OR 0.52; [95% CI: 0.09-2.85])
- There were no fatal bleeding events and there were no cases of intracranial hemorrhage
- Meta-analysis of RAPID and mpRCT of therapeutic anticoagulation in moderately patients with COVID-19 did not provide conclusive evidence for a reduction in mortality but may improve organ support-free days and ventilator free-days alive.

**Limitations:**
- Open-label, adaptive design.
- Significant overlap between regimens used in the two groups- eight different interventions used (not equivalent to each other), including combination aspirin.
- Control group was mostly split between low-dose and intermediate-dose anticoagulation.
- However, only 79% of patients in the therapeutic group received full therapeutic dose anticoagulation (8.7% subtherapeutic dosing, 5.8% low-dose, 5.8% intermediate dose).

**A subset of patients A subset of patients in the REMAP-CAP platform underwent randomization to other platform domains, including an antiplatelet domain.**
<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Lopes (ACTION), June 2021&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Pragmatic, open-label, multi-center, randomized controlled trial among 615 hospitalized patients across 31 sites in Brazil between June 2020 and February 2021</td>
<td>1:1 Randomization to therapeutic anticoagulation (rivaroxaban 20 mg once daily or enoxaparin 1 mg/kg SQ BID or heparin IV per protocol if unstable; n=311) or standard prophylaxis (enoxaparin or heparin; n=304). All patients in the therapeutic group continued prophylaxis (enoxaparin or heparin; n=311) or standard anticoagulation plus statin or placebo 1:1 randomization to intermediate dose or standard dose anticoagulation plus placebo. Patient selection: Mean age 60, male 56.8%, man BMI 30.3 Mean baseline D-Dimer 2.3 x ULN and mean SCr 85.2 mmol/L Mean duration from symptom onset to hospitalization 7.1 days Mean mean duration from hospitalization to randomization 1.4 days Mean mean treatment duration was 6.5 and 6.3 days in therapeutic and prophylactic treatment groups, respectively Concomitant baseline antiplatelet agents (in 12% of the patients) and glucocorticoids (70%). No patients were on remdesivir or tocilizumab at baseline Anticoagulant drug: enoxaparin 98.2% in therapeutic group while 93.7% of patients received heparin for prophylaxis. Dosing regimens and percentage of patients achieving full anticoagulation not described.</td>
<td>Primary outcome: No statistically significant difference - No differences in composite thrombotic outcome and all-cause death were observed between groups (15% vs 14%; RR 1.03; [95% CI: 0.70-1.50]; p=0.91) Secondary outcome: No statistically significant difference - No differences in rehospitalization rates (1% vs 2%; RR 0.39; [95% CI: 0.08-2.01]; p=0.28) or WHO ordinal scale at end of 30 days (OR 1.35; [95% CI: 1.61-8.27]; p=0.0010) Safety outcome: Major or clinically relevant non-major bleeding through 30 days was significantly higher for those treated with therapeutic anticoagulation compared to prophylactic dosing (8% vs 2%; RR 3.64; [95% CI: 1.61-8.27]; p=0.0010) Adverse events: Allergic reaction to the study medication occurred in two (1%) patients in the therapeutic anticoagulation group and three (1%) in the prophylactic anticoagulation group. There was no net benefit to full dose anticoagulation in moderately ill patients compared to standard prophylaxis at the cost of increased major bleeding. Limitations: Open-label, adaptive design. Patient care protocols may vary among different countries that participated in the study.</td>
</tr>
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</table>

Sadeghpour (INSPIRATION), March 2021<sup>2</sup> | Multicenter, randomized, open-label, 2x2 factorial, clinical trial among 562 ICU patients across 10 academic centers in Iran Between July 29, 2020 and November 19, 2020 | 1:1 randomization to intermediate dose or standard dose anticoagulation plus statin or placebo. Patient selection: Mean age 56.6, BMI 30.3, most common comorbid conditions DM (25%) and HTN (50%), 80% never smokers Mean time from symptom onset to randomization 10 days 83% classified as moderate disease; supplemental oxygen 75%, stable condition 95% Baseline D-Dimer level: >1 x ULN (100%); ≥3 ULN (27%) Concomitant baseline therapies included antiplatelet agents (in 8% of the patients), vasopressor (5%), and corticosteroids (83%) Anticoagulant drug (therapeutic (n=1181: rivaroxaban 90%, enoxaparin 10%) vs prophylaxis (n=1050): enoxaparin 84%, heparin 16%) | Primary outcome: No statistically significant difference - Adjudicated acute arterial thrombosis, (VTE), ECMO, all-cause death at 30 days (45.7% vs 44.1%; OR 1.06 [95% CI: 0.76-1.48]; p=0.70) Secondary outcome: No statistically significant difference - All-cause mortality (43.1% vs 40.9%; OR 1.09 [95% CI: 0.78-1.53]; p=0.50) - Objectively confirmed VTE (3.3% vs 3.5%; OR 0.93 [95% CI: 0.37-2.32]; p=0.87) - Median ventilator free days (30 [3-30] vs 30 [1-30]; p=0.50) Adverse events: | Limitations: Among patients admitted to the ICU with COVID-19, intermediate-dose prophylactic anticoagulation, failed to result in a significant difference in venous or arterial thrombosis, need for ECMO, or 30-day mortality compared...
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Results</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Meta-analysis of 8 RCTs (INSPIRATION, Perepu et al, HESACOVID, ACTION, RAPID, ATTACC, ACTIV-4a, REMAP-CAP, HEP-COVID) including 5580 patients</td>
<td>Major bleeding (2.5% vs 1.4%; OR 1.83 [95% CI: 0.53-5.93]; p=0.33)</td>
<td>Clinical outcome: No statistically significant difference</td>
<td></td>
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<tr>
<td></td>
<td>Clinically relevant non-major bleeding (4.3% vs 1.7%; OR 2.55 [95% CI: 0.92-7.04]; p=0.07)</td>
<td>Data on all-cause mortality measured at 28 days and in-hospital showed little or no effect on the pooled population of patients with moderate and severe COVID-19 (RR 0.68; [95% CI: 0.32-1.42]; I2=74%)</td>
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<tr>
<td></td>
<td>Severe thrombocytopenia (2.2% vs 0%; p=0.01)</td>
<td>Subgroup analysis of patients with moderate COVID-19, therapeutic anticoagulation showed benefit for all-cause mortality at 28 days based on the RAPID trial with 465 participants, whereas, little or no effect was shown for in-hospital mortality based on the large ATTACC, ACTIV-4a, REMAP-CAP platform trial with 2226 participants</td>
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</table>

**Patient Selection**
- Median age 62, female (42.2%), median BMI 27, median days of symptoms prior to hospitalization 7, median duration of hospitalization before randomization 4 days, mechanical ventilation (20%), concomitant aspirin (30%), remdesivir (60%), corticosteroid (93%), vasopressors (22%), D-dimer (1037 ng/ml vs 910 ng/ml), FiO2 > 50% (41%)

**Possible Regimens:**
- Intermediate dose
  - Enoxaparin 1 mg/kg daily OR 0.6 mg/kg BID for wt ≥120 kg or BMI ≥ 35
  - For CrCl 15 to 30 ml/min: 0.5 mg/kg daily (at least 40 mg)
  - For CrCl ≤15 ml/min: UFH 10,000 units SC BID
- Standard dose
  - Enoxaparin 40 mg sc daily OR 40 mg BID for wt ≥120 kg or BMI ≥ 35
  - For CrCl 15 to 30 ml/min: 30 mg daily For CrCl ≤15 ml/min: UFH 5,000 units SC BID

**Systematic Review and Meta-Analyses (RCTs and Observational Cohorts)**

- **Study:** Reis, Dec 2021
- **LOE:** 1b, n = 5580

<table>
<thead>
<tr>
<th>Included</th>
<th>Study Design</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Adults ≥18 years with confirmed COVID-19 admitted to ICU within 7 days of initial hospitalization</td>
<td>Clinical outcome: No statistically significant difference</td>
<td></td>
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<tr>
<td>Without firm indication for anticoagulation (e.g., mechanical valve, high-risk AF, VTE, or LV thrombus) and estimated survival ≥ 24 hours</td>
<td>Data on all-cause mortality measured at 28 days and in-hospital showed little or no effect on the pooled population of patients with moderate and severe COVID-19 (RR 0.68; [95% CI: 0.32-1.42]; I2=74%)</td>
<td></td>
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<tr>
<td>Exclusion</td>
<td>Safety outcome: Therapeutic-dose anticoagulation showed a non-significantly higher rate of major bleeding events in the subgroups (RR 1.78; [95% CI: 1.15-2.74])</td>
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<tr>
<td>Weight &lt; 40 kg</td>
<td>However, the pooled effect reported a sufficient number of events and patients which reached statistical significance (RR 1.78; [95% CI: 1.15-2.78]; I2=0%)</td>
<td></td>
</tr>
<tr>
<td>Weight &gt;120 kg or BMI &gt; 35 AND CrCl &lt; 30 ml/min</td>
<td>Limitations: Certainty of evidence on whether intermediate- or therapeutic-dose anticoagulation compared to standard thromboprophylaxis is beneficial or not is still low for hospitalized COVID-19 patients.</td>
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<tr>
<td>Use of systemic anticoagulation for another indication (see above)</td>
<td>Results of this meta-analysis indicate that moderately affected COVID-19 patients may benefit from therapeutic-dose anticoagulation, but not patients with severe COVID-19.</td>
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</tr>
<tr>
<td>Known major bleeding within 30 days</td>
<td>The risk for bleeding is increased independent of disease severity.</td>
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<tr>
<td>PLT &lt; 50</td>
<td>Limitations: Conflicting results and lack of evidence that would warrant high certainty, due to the wide heterogeneity of study settings, populations, and therapeutic approaches.</td>
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<tr>
<td>Pregnancy</td>
<td>Disease severity as well as prophylactic and anticoagulation dosages were</td>
<td></td>
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<tr>
<td>History of HIT(T)</td>
<td>not widely standardized.</td>
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<tr>
<td>Ischemic stroke within 2 weeks</td>
<td><strong>Possible Regimens:</strong></td>
<td></td>
</tr>
<tr>
<td>Major head or spinal trauma in past 30 days</td>
<td>Intermediate dose</td>
<td></td>
</tr>
<tr>
<td>Craniotomy/major neurosurgery within past 3 months</td>
<td>- Enoxaparin 1 mg/kg daily OR 0.6 mg/kg BID for wt ≥120 kg or BMI ≥ 35</td>
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<tr>
<td>Known brain mets or malformations</td>
<td>- For CrCl 15 to 30 ml/min: 0.5 mg/kg daily (at least 40 mg)</td>
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<tr>
<td>Epidural, spinal or pericardial catheter</td>
<td>- For CrCl ≤15 ml/min: UFH 10,000 units SC BID</td>
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<tr>
<td>Major surgery within 14 days</td>
<td>Standard dose</td>
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<tr>
<td>Allergy to study medications or withdrawal of consent</td>
<td>- Enoxaparin 40 mg sc daily OR 40 mg BID for wt ≥120 kg or BMI ≥ 35</td>
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<tr>
<td>Additional criteria for statins</td>
<td>- For CrCl 15 to 30 ml/min: 30 mg daily For CrCl ≤15 ml/min: UFH 5,000 units SC BID</td>
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</tbody>
</table>

**Limitations:**
- Open-label.
- Benefit in non-critically ill patients remains unknown.
- Compared 8 different regimens of 2 drugs in 2 patient groups.
- Used once daily regimen (high peaks, low troughs).

**Additional criteria for statins:**
- Known major bleeding within 30 days
- PLT < 50
- Weight >120 kg or BMI > 35
- Known brain mets or malformations
- Epidural, spinal or pericardial catheter
- Major surgery within 14 days
- Allergy to study medications or withdrawal of consent
- Additional criteria for statins

**Study Population and Regimen:**
- INSPIRATION (n=562) intermediate vs standard in critically ill patients
- ACTION (n=614) therapeutic vs standard with rivaroxaban non-critically ill patients and enoxaparin in critically ill patients
- REMAP-CAP, ACTIVE-4a, ATTACC (n=1098) therapeutic vs standard LMWH/UFH in critically ill patients
- REMAP-CAP, ACTIVE-4a, ATTACC (n=2219) therapeutic vs standard LMWH/UFH in non-critically ill patients
- HESACOVID (n=20) therapeutic vs standard LMWH/UFH in critically ill patients

**Results:**
- Major bleeding (2.5% vs 1.4%; OR 1.83 [95% CI: 0.53-5.93]; p=0.33)
- Clinically relevant non-major bleeding (4.3% vs 1.7%; OR 2.55 [95% CI: 0.92-7.04]; p=0.07)
- Severe thrombocytopenia (2.2% vs 0%; p=0.01)
### Study Design

<table>
<thead>
<tr>
<th>Study</th>
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<th>Results</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>RAPID (n=465)</td>
<td>therapeutic vs standard LMWH/UFH in non-critically ill patients</td>
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<tr>
<td>HEP-COVID (n=257)</td>
<td>therapeutic vs standard LMWH/UFH in non-critically ill patients</td>
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<tr>
<td>Perepu et al (n=176)</td>
<td>intermediate dose vs standard dose LMWH/UFH in critically ill patients</td>
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<td>not defined in a standardized way in the studies.</td>
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</tbody>
</table>

Zhang, Nov 2021

Meta-analysis of 42 clinical trials (6 RCTs, 36 retrospective cohorts) encompassing 28,055 assessing the safety and efficacy of intermediate-to-therapeutic anticoagulation vs prophylaxis in hospitalized patients with COVID-19

13 studies were performed exclusively in ICU patients. 18 studies originated from the US, 2 were international

UFH and LMWH were the main anticoagulants used

<table>
<thead>
<tr>
<th>Primary outcome: No statistically significant difference</th>
<th>Secondary outcome:</th>
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<tbody>
<tr>
<td>Intermediate-to-therapeutic anticoagulation did not significantly reduce all-cause mortality (RR 1.12; [95% CI: 0.99-1.25]; p=0.06; I²=77%)</td>
<td>Intermediate-to-therapeutic anticoagulation was significantly associated with an increased incidence of any bleeding events when compared to prophylactic anticoagulation (RR 2.16; [95% CI: 1.79-2.60]; p&lt;0.01; I²=31%). Moderate heterogeneity was noted among the 27 included studies</td>
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<tr>
<td>Sub-group analyses of critically ill ICU patients also revealed no difference in mortality compared to prophylactic anticoagulation, with less heterogeneity noted among the 11 studies evaluated (RR 0.94; [95% CI: 0.79-1.10]; p=0.40; I²=30%)</td>
<td>Subgroup analyses of critically ill patients also demonstrated higher any bleeding events with low heterogeneity (RR 2.11; [95% CI: 1.77-2.51]; p=0.01; I²=11%)</td>
</tr>
<tr>
<td>Major bleeding events were increased significantly (RR 2.11; [95% CI: 1.77-2.51]; p&lt;0.01; I²=11%)</td>
<td>No difference in thrombotic complications were observed between groups (RR 1.30; [95% CI: 0.79-2.15]; p=0.30; I²=88%)</td>
</tr>
<tr>
<td>No difference in thrombotic complications were observed between groups (RR 1.30; [95% CI: 0.79-2.15]; p=0.30; I²=88%)</td>
<td>Subgroup analyses of critically ill patients demonstrated lower thrombotic complications with intermediate-to-therapeutic anticoagulation compared to prophylaxis dosing with low heterogeneity (RR 0.71; [95% CI: 0.56-0.89]; p=0.03; I²=0%)</td>
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</table>

Given insignificant survival benefit and increased risk of major bleeding events, prophylactic dose anticoagulation is preferred over intermediate-to-therapeutic anticoagulation among unselected hospitalized with COVID-19 patients.

Limitations:
- Majorly of included studies were retrospective cohorts.
- Potential for selection bias.
- Anticoagulants, dosing, and treatment duration, and follow up period varied widely across studies.
- Patients with higher disease severity and risk of thrombotic events were more likely to be treated with intermediate-to-therapeutic anticoagulation.
- Low quality evidence and high heterogeneity noted for non-ICU mortality and thrombotic outcomes.
- Evidence was of moderate quality for ICU patients.

Giossi, Sept 2021

Meta-analysis of 33 studies (31 observational, 2 RCT) were included for a total of 32,688 patients examining the effectiveness of LMWH, UFH, or fondaparinux in COVID-19 patients

Quality assessment showed a general low quality of observational studies

Treatment of heparins 66.5% (n=21,723) vs not treated with heparins 33.5% (n=10,965)

<table>
<thead>
<tr>
<th>Primary outcome:</th>
<th>Secondary outcome:</th>
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<tr>
<td>Both prophylactic dose and full dose resulted in reduction in all-cause mortality among 31 included studies (HR 0.63; [95% CI: 0.57-0.69] and HR 0.56; [95% CI: 0.47-0.66], respectively)</td>
<td>No difference in length of stay were noted between groups. However, full dose heparin was associated with higher risk of major bleeding (OR 2.01; [95% CI: 1.14-3.53])</td>
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<tr>
<td>No significant difference was found between the two strategies (-2.38; [95% CI: -3.14 to -1.61])</td>
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Full and prophylactic dose is effective in reducing mortality in hospitalized COVID-19 patients, compared to no treatment. However, no significant difference was found between the two strategies.

Full heparin dose was associated with an increased risk of bleeding.

Limitations:
- Majority of included studies were retrospective cohorts.
- Observational studies were of low quality evidence.
- Severity of illness varied significantly among studies.
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<tr>
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<th>Study Design</th>
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</table>
| **Ortega Paz, Sept 2021**<sup>13</sup> <br>LOE 1b, n = 5154 | **Meta-analysis of 7 randomized controlled trials** (INSPIRATION, ACTION, REMAP-CAP, ACTIV-4a, ATTACC, HESACOVID, RAPID) encompassing 5154 patients for a mean follow-up period of 33 days | **Primary outcome:**  
- Compared to standard dose prophylaxis, escalated-dose anticoagulation was not associated with reduction in all-cause mortality (RR 0.96; [95% CI: 0.78-1.18]; I²=56%) but was associated with higher risk of major bleeding (RR 1.73; [95% CI: 1.15-2.60]; I²=0%)  
**Secondary outcome:**  
- Escalated dose regimen was associated with reduction in VTE but not lower rates of VTE (RR 0.39; [95% CI: 0.26-0.58]; I²=0%) and RR 1.03; [95% CI: 0.60-1.75]; I²=0%, respectively)  
- No difference in incidence of MI, stroke, or systemic arterial embolism were observed  
- However, escalated dose anticoagulation was associated with higher rates of any bleeding and minor bleeding compared to prophylactic dose regimen bleeding (RR 2.01; [95% CI: 1.08-3.74]; I²=47%) and RR 2.23; [95% CI: 1.04-4.81]; I²=30%, respectively)  
- Subgroup analysis showed consistent results for all included outcomes among both critically ill and non-critically ill patients, except for any bleeding, which was significantly higher in non-critically ill, but not in critically ill patients | - High heterogeneity among anticoagulation regimen.  
- Rationale for treatment assignment was not uniform across studies.  
- Escalated dose anticoagulation was not associated with reduced all-cause mortality but was associated with a higher risk of bleeding compared to standard dose prophylaxis.  
- The NNT for all-cause death was 119, whereas the NNH for major, minor, and any bleeding events were 102, 32, and 16, respectively.  
**Limitations:**  
- Meta-analysis did not include more recently published RCTs (X-COVID-19 HEP-COVID)  
- High heterogeneity noted with mortality outcome, zero heterogeneity noted for safety outcome.  
- ACTION used rivaroxaban but sensitivity analyses remained the same after exclusion.  
- INSPIRATION and Perepu et al. used intermediate dose anticoagulation, study findings were consistent after removal.  
- Cannot rule out risk of publication, reporting, and ecological biases. |
| **Kamel, Oct 2020**<sup>14</sup> <br>LOE 1b, n = not fully described, varied based on analyses | **Systematic review and meta-analysis of 19 controlled, non-randomized studies** (16 retrospective cohorts, 3 prospective cohorts, and 1 case-control study).  
Overall quality of studies were poor with only 5 considered good  
UFH and LMWH were the main anticoagulants used, while DOACs were included in 4 of the studies  | **Primary outcome:**  
- Use of anticoagulation (prophylactic or therapeutic) was associated with lower mortality in the current meta-analysis (RR 0.57; [95% CI: 0.35-0.94]; I²=87%).  
- No difference in mortality was observed when prophylactic anticoagulation was compared to therapeutic anticoagulation (RR 1.58; [95% CI: 1.34-1.87])  
**Secondary outcome:**  
- Incidence of PE, DVT and VTE combined (not performed due to small number of studies)  
- No association between pre-admission anticoagulant on mortality or incidence of VTE was demonstrated (RR 0.84; [95% CI: 0.49-1.43]; p>0.05)  | - Both therapeutic and prophylactic anticoagulation was associated with mortality reduction in COVID-19.  
- No differences were observed between those that received prophylactic dosing vs therapeutic anticoagulation.  
**Limitations:**  
- Included only observational studies (two pre-prints; Results of RCTs not available at the time of study).  
- Low-quality studies.  
- Selection bias and confounding suspected due to non-randomized, retrospective design. |
**Study** | **Study Design** | **Results** | **Conclusions**
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McBane, Aug 2020\^15 | Systematic review and meta-analysis of 37 non-randomized studies (36 observational retrospective cohorts, 1 prospective) across 6 countries with the majority from China (28), followed by France (3), Italy (2), Netherlands (2), Ireland (1), and the United States (1) 8 were conducted in ICU setting; 29 non-specific inpatient setting; Overall mortality was as high as 56% | Incidence of Thrombotic Events:  
- Meta-analyses of the frequency of thrombotic events ranging from 1% (myocardial infarction) to 17% (PE)  
- An overall VTE rate was not pooled across studies because of high heterogeneity  
Effect of Anticoagulation:  
- No difference in mortality was observed for those treated with anticoagulation (OR, 0.99; [95% CI: 0.82-1.19]; I²=0%) | Dose not specified in all the studies.  
Various anticoagulants, doses, and patient populations described.  
Pooled estimates not calculated for VTE due to small sample size.  
Algorithmic Guidance provided for prevention and management of thrombosis based on expert opinion, low-certainty evidence.  
Limitations:  
- Included only observational studies (Results of RCTs not available at the time of study).  
- Most reported series are limited to ICU patients.  
- Few reports exist regarding bleeding outcomes between prophylactic and therapeutic dosing.  
- Few meta-analyses reported, mostly synthesized review paper.  
Overall heterogeneity was moderate to high.

References