Anticoagulation Literature Review: COVID-19 Clinical Advisory Group Update
April 2021

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 Trials:
  - Findings from a conglomerate of three open-label, pragmatic, adaptive, multiplatform, multicenter, randomized controlled trials (REMAP-CAP, ACTIV-4a, and ATTACC) 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 (3.1% vs 2.4%; p=0.6) and lower risk of major thrombotic events (5.7% vs 10.3%; p=0.012).
  - Results from the INSPIRATION randomized clinical trial do not support the routine empirical use of intermediate-dose prophylactic anticoagulation in unselected ICU patients with COVID-19.
  - The potential protective effect of antiplatelet agents in hospitalized patients with COVID-19 is being evaluated in 11 RCTs.
- Systematic Review and Meta-Analyses:
  - Synthesized evidence from low-quality, observational studies suggest standard thromboprophylaxis may reduce mortality in COVID-19 patients and therapeutic anticoagulation may offer an advantage over prophylactic dosing for some patients.
- Guideline Recommendations:
  - Anticoagulation Forum (May 2020): We recommend pharmacologic VTE prophylaxis for all hospitalized patients with confirmed or highly suspected COVID-19, regardless of VTE risk assessment score.
    - For all non-critically ill hospitalized patients (i.e., not in an ICU) with confirmed or highly suspected COVID-19, we recommend standard dose VTE prophylaxis as per existing societal guidelines for medically ill and surgical hospitalized patients. Dose adjustments for renal function or extremes of weight should follow product labeling and/or institutional protocols.
    - For critically ill patients (i.e., in an ICU) with confirmed or highly suspected COVID-19, we suggest increased doses of VTE prophylaxis (e.g., enoxaparin 40 mg subcutaneous twice daily, enoxaparin 0.5 mg/kg subcutaneous twice daily, heparin 7500 units subcutaneous three times daily, or low-intensity heparin infusion (Expert Opinion).
      - For patients that are improving and transferring out of the ICU to the medical ward, it is reasonable to de-escalate to standard VTE prophylaxis dosing.
  - ISTH (May 2020):
    - VTE prophylaxis in non-ICU hospitalized COVID-19 patients: A universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent. Intermediate-dose LMWH may also be considered (30% of respondents).
    - VTE prophylaxis in sick ICU hospitalized COVID-19 patients: Routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk. Intermediate-dose LMWH (50% of respondents) can also be considered in high risk patients. Patients with obesity as defined by actual body weight or BMI should be considered for a 50% increase in the dose of thromboprophylaxis. Treatment-dose heparin should not be considered for primary prevention until the results of randomized controlled trials are available.
  - CHEST (June 2020): In the absence of a contraindication, in hospitalized patients acutely or critically ill with COVID-19, we suggest anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis. We suggest anticoagulant thromboprophylaxis with LMWH over anticoagulant thromboprophylaxis with UFH; and we recommend anticoagulant thromboprophylaxis with LMWH or UFH over anticoagulant thromboprophylaxis with fondaparinux or a DOAC.
    - In critically ill or acutely ill hospitalized patients with COVID-19, we recommend current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment doses, per existing guidelines.
    - In critically ill or acutely ill hospitalized patients with COVID-19, we recommend against the use of antiplatelet agents for VTE prevention.
  - SCCM (January 2021): For adults with severe or critical COVID-19, we recommend using pharmacologic VTE prophylaxis over not using prophylaxis (Strong).
  - For adults with severe or critical COVID-19 and no evidence of VTE, we suggest against the routine use of therapeutic anticoagulation outside of clinical trials (Weak).
  - WHO (January 2021): A conditional recommendation to use thromboprophylaxis dosing of anticoagulation rather than intermediate or therapeutic dosing in patients hospitalized with COVID-19, without an established indication for higher dose of anticoagulation (very low certainty).
  - NIH (February 2021): Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation (AIII). For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated (BIII).
    - There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.
  - American Society of Hematology (February 2021): The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects).
    - An individualized assessment of the patient’s risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding risk.

Recommendations:
- Results from recent RCTs fail to provide any definitive conclusions on the most appropriate VTE prophylaxis strategy for COVID-19 patients. Interim results from these trials have not been adjudicated or peer-reviewed and should be interpreted with appropriate caution.
- Based on the totality of data to date, most guidelines and guidance documents favor the use of standard prophylactic anticoagulation for most hospitalized patients with COVID-19. Use of intermediate or therapeutic doses of anticoagulation for the purpose of thromboembolism prophylaxis should be done selectively and (preferably) in the setting of a clinical trial whenever possible.
- Clinicians should continue to weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients.
### Study Design

**REMAP-CAP, ACTIV-4a, ATTACC**, Mar 2021
LOE 1b, n=1074

<table>
<thead>
<tr>
<th>REMAP-CAP, ACTIV-4a, ATTACC</th>
<th>Conglomerate of 3 multicenter, open-label, randomized controlled trials of 1074 hospitalized patients with severe, confirmed COVID-19 between April 2020 and December 2020.</th>
<th><strong>Randomized Controlled Trials</strong></th>
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<tbody>
<tr>
<td><strong>1:1 Randomization (ACTIV-4a) or response-adaptive randomization (REMAP-CAP and ATTACC) to therapeutic anticoagulation (n=532) or usual care pharmacological thromboprophylaxis (n=557) according to local site protocols for up to 14 days or recovery</strong></td>
<td>Inclusion required admission to the ICU within &lt;48 hours (REMAP-CAP) or admission to the hospital within &lt;72 hours (ACTIV-4a, ATTACC). Detailed inclusion and exclusion criteria not described.</td>
<td><strong>Primary outcome: No statistically significant difference</strong></td>
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<td><strong>Possible Regimens:</strong></td>
<td>- Low dose thromboprophylaxis</td>
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<tr>
<td>- Enoxaparin 40mg daily, possible 40 mg BID for BMI ≥40, 30 mg daily for CrCI &lt; 30 ml/min</td>
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<td>- Dalteparin 5000 units daily, possible 7500 units daily for BMI ≥40</td>
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<td>- Tinzaparin 75 units/kg or 4500 once daily, possible 8000 units daily for BMI ≥40</td>
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<tr>
<td>- Heparin 5000 units BID or TID; possible 7500 units BID for BMI ≥40</td>
<td>- No difference in median organ support free days (therapeutic 3 [-1.16] vs. usual care 5 [-1.16]; aOR 0.87 [95% CI: 0.70-1.08])</td>
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<td><strong>Secondary outcome:</strong></td>
<td>- Probability of futility 99.8% and inferiority 89.4%</td>
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<td>- 90-day survival (64.3% vs 65.9%; aOR 0.88 [95% CI:0.67-1.16]). Probability of inferiority 81.0%</td>
<td>- No statistically significant difference</td>
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<td><strong>Adverse events:</strong></td>
<td>- Major bleeding events (3.1% vs 2.4%)</td>
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### Results

**Study Design**

**LOE 1b, n=562**

- 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

- **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)

- **Conclusions**
  - In critically ill COVID-19 patients, therapeutic anticoagulation offered no additional benefit compared to low or intermediate-dose thromboprophylaxis with a high probability of inferiority (89%)
  - It remains unknown if therapeutic anticoagulation is beneficial over low or intermediate dose thromboprophylaxis in non-critically ill patients. A press release from January 22, 2021 suggests superiority of anticoagulation for moderately ill patients (n=2248) included in this conglomeration
  - Whether intermediate dose is superior to standard low-dose prophylaxis in critically ill patients also remains uncertain

### Limitations:

- Pre-publication, not yet peer reviewed
- Open-label design
- Pragmatic design
- Significant overlap between heparin 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 78% of patients in the therapeutic group received full therapeutic dose anticoagulation (7.8% subtherapeutic dosing, 3.6% low-dose, 10.9% intermediate dose)
- Selection of patients may not benefit from therapeutic anticoagulation (low D-dimer)

- Among patients admitted to the ICU with COVID-19, intermediate-dose prophylactic anticoagulation, failed to result in a significant difference in venous or arterial
**Study Design**

1:1 randomization to intermediate dose or standard dose anticoagulation plus statin or placebo

**Included**
- Adults ≥18 years with confirmed COVID-19 admitted to ICU within 7 days of initial hospitalization
- Without firm indication for anticoagulation (e.g. mechanical valve, high-risk AF, VTE, or LV thrombus) and estimated survival ≥ 24 hours

**Exclusion**
- Weight < 40 kg
- Weight >120 kg or BMI > 35 AND CrCl < 30 ml/min
- Use of systemic anticoagulation for another indication (see above)
- Known major bleeding within 30 days
- PLT < 50
- Pregnancy
- History of HIT(T)
- Ischemic stroke within 2 weeks
- Major head or spinal trauma in past 30 days
- Cranectomy/major neurosurgery within past 3 months
- 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

**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

**Results**

- 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:**
  - 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)**

- **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%)

**Conclusions**

- 3.3% vs 3.5% Objectively confirmed VTE
- Median ventilator free days (30 [3-30] vs 30 [1-30]; p=0.50)

- **Adverse events:**
  - 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)**

**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)

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

**Kamel, Oct 2020**

LOE 1b, n= not fully described, varied based on analyses

- **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:**
  - Both therapeutic and prophylactic anticoagulation was associated with mortality reduction in COVID-19
  - No differences were observed between those that received thrombosis, need for ECMO, or 30-day mortality compared with standard-dose prophylaxis
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<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
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<th>Conclusions</th>
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| McBane, Aug 2020 | 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) | - 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%) | Algorithmic Guidance provided for prevention and management of thrombosis based on expert opinion, low-certainty evidence |
| McBane, Aug 2020 | 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 | - 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) | Prophylactic dosing vs therapeutic anticoagulation |
| McBane, Aug 2020 | 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% | |