Use of Anticoagulation in Patients with COVID-19

An Educational Slide Set
American Society of Hematology 2021 Guidelines on Use of Anticoagulation in Patients with COVID-19

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Clinical Guidelines

American Society of Hematology 2021 Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19

ASH Clinical Practice Guidelines on VTE

1. Prevention of VTE in Surgical Hospitalized Patients
2. Prophylaxis in Hospitalized and Non-Hospitalized Medical Patients
3. Treatment of Acute VTE (DVT and PE)
4. Optimal Management of Anticoagulation Therapy
5. Prevention and Treatment of VTE in Patients with Cancer
6. Heparin-Induced Thrombocytopenia (HIT)
7. Thrombophilia
8. Pediatric VTE
9. VTE in the Context of Pregnancy
10. Diagnosis of VTE
11. Use of Anticoagulation in Patients with COVID-19
### How were these ASH guidelines developed?

<table>
<thead>
<tr>
<th>PANEL FORMATION</th>
<th>CLINICAL QUESTIONS</th>
<th>EVIDENCE SYNTHESIS</th>
<th>MAKING RECOMMENDATIONS</th>
</tr>
</thead>
</table>
| Each guideline panel was formed following these key criteria:  
  - Balance of expertise (including disciplines beyond hematology, and patients)  
  - Close attention to minimization and management of COI | 2 clinically-relevant questions generated in PICO format  
(population, intervention, comparison, outcome) | Evidence summary generated for each PICO question via systematic review of health effects plus:  
  - Resource use  
  - Feasibility  
  - Acceptability  
  - Equity  
  - Patient values and preferences | Recommendations made by guideline panel members based on evidence for all factors.  
  - The guidelines will be updated using a living recommendation approach as new evidence becomes available. |

**Example: PICO question**  
"In patients with COVID-19 related critical illness who do not have suspected or confirmed VTE, should intermediate- or therapeutic intensity anticoagulation versus prophylactic-intensity anticoagulation be used for thromboprophylaxis?"
How patients and clinicians should use these recommendations

<table>
<thead>
<tr>
<th></th>
<th><strong>STRONG Recommendation</strong></th>
<th><strong>CONDITIONAL Recommendation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&quot;The panel recommends...&quot;)</td>
<td>(&quot;The panel suggests...&quot;)</td>
</tr>
<tr>
<td>For patients</td>
<td>Most individuals would want the intervention.</td>
<td>A majority would want the intervention, but many would not.</td>
</tr>
<tr>
<td>For clinicians</td>
<td>Most individuals should receive the intervention.</td>
<td>Different choices will be appropriate for different patients, depending on their values and preferences. Use <strong>shared decision making</strong>.</td>
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</table>
Patient groups addressed in this chapter

**Acutely Ill Medical Patient**
Patients hospitalized for medical illness

**Critically Ill Patient**
Patients suffering from immediately life-threatening illness requiring admission to intensive care unit
What these guidelines are about

Anticoagulants carry **benefits** (reducing venous thromboembolism) and **risks** (life-threatening bleeding)

Recognizing and **mitigating risk for harm** from anticoagulants requires evidence-based approach to management

This guideline focuses on **anticoagulant dose intensity** for critically ill and acutely ill hospitalized patients with COVID-19 who do not have suspected or confirmed venous thromboembolism
Objectives

By the end of this session you will be able to:

1. Describe VTE prophylaxis recommendations for hospitalized patients with COVID-19 related critical illness who do not have suspected or confirmed VTE
   • Intermediate- or therapeutic-intensity versus prophylactic intensity anticoagulation

2. Describe VTE prophylaxis recommendations for hospitalized patients with COVID-19 related acute illness who do not have suspected or confirmed VTE
   • Intermediate- or therapeutic-intensity versus prophylactic intensity anticoagulation
Methods

Overall
• GRADE methodology for guideline recommendation development
• Cochrane methodology for systematic reviews

Initial Phase
• PICO question generation and prioritization
• Selection of critical outcomes
• Systematic review for baseline risk estimates
• Systematic review for effect of different anticoagulation intensities

Living Phase
• Monthly updated searches for baseline risk estimates and prognostic factors
• Monthly updated searches for effect of different anticoagulation strategies
• Revisiting guideline recommendations if new evidence meets pre-specified criteria
Formulate question
Assess single studies

Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important

Synthesize and Create evidence profile & Evidence to Decision Table with GRADEpro
Rate certainty of evidence for each outcome and other criteria

Recommendation/Decision
Guideline/coverage decision

Grade recommendations (Evidence to Recommendation)
- For or against (direction)
- Strong or conditional/weak (strength)

Evidence to decision or recommendation framework

Published October 8, 2020 – New Evidence Available in Blood Advances
PICO Question Generation & Prioritization

- Brainstorming: inclusive list of potential PICO questions to address
- Importance rating: selecting the PICO questions with the most critical importance
Outcome Selection

• Brainstorming: inclusive list of potential outcomes to address
• Importance rating: selecting the most critical outcomes for key stakeholders
  ➢ Using Health Outcome Descriptors (marker states) - [https://ms.gradepro.org/](https://ms.gradepro.org/)

Critical Outcomes

- All-cause mortality
- Pulmonary embolism
- Deep venous thrombosis
- Major bleeding
- Multi-organ failure
- Ischemic stroke

- Intracranial hemorrhage/hemorrhagic stroke
- Invasive mechanical ventilation
- Limb amputation
- ICU admission
- ST-elevation myocardial infarction
Evidence for Effect of the Intervention

Baseline Risk: 5 per 1,000
Relative Effect: RR = 0.40
Absolute Effect: 3 per 1,000 fewer
**GRADE Certainty of Evidence**

**Table: Grade's approach to rating quality of evidence (aka confidence in effect estimates)**

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1. **Establish initial level of confidence**
   - **Study design**
     - Randomized trials ► High Confidence
     - Observational studies ► Low confidence

2. **Consider lowering or raising level of confidence**
   - **Reasons for considering lowering or raising confidence**
     - **▼Lower if**
       - Risk of Bias: Large effect, Dose Response
       - Inconsistency: All plausible confounding & bias
       - Indirectness: Would reduce a demonstrated effect or
       - Imprecision: Would suggest spurious effect if no effect was observed
     - **▲Higher if**

3. **Final level of confidence rating**
   - **Confidence in an estimate of effect across these considerations**
     - High ●●●●
     - Moderate ●●●
     - Low ●●
     - Very Low ●

*upgrading criteria are usually applicable to observational studies only.*
Baseline Risk – Systematic Review

• Incidence rate of selected outcomes:
  • In the two populations of interest
  • Among patients receiving prophylactic intensity anticoagulation

• Required:
  • Not high risk of bias (according to simplified QUIPS)
  • Reporting duration of follow-up

• Initial search date: 23-JUL-2020
• Screened: 14,816 citations
• Included: 51 Studies

• Analysis:
  • Pooled estimates using generalized linear mixed model
  • Descriptive, if only one study identified, or when pooling was considered inappropriate
Effect of Anticoagulation – Systematic Review

• Comparison of two or more anticoagulation intensities for prevention of VTE:
  • In the two populations of interest
  • Primarily addressing Prophylactic vs. Intermediate/Therapeutic intensity

• Required:
  • Pre-defined definitions for Prophylactic, Intermediate, Therapeutic intensity
  • Risk of bias assessed with ROBINS-I

• Initial search date: 20-AUG-2020
• Screened: 3,118 citations
• Included: 12 Studies

• Analysis:
  • Descriptive analysis of adjusted relative effect estimates
  • Pooling unadjusted relative effect estimates in meta-analysis
Evidence for Other Domains

• The panel considered additional Evidence-to-Decision domains to generate the recommendations:
  • Resource use
  • Cost-effectiveness
  • Health equity
  • Acceptability
  • Feasibility

• Evidence for these domains was also sought in the two reviews

• COVID-19 specific evidence not yet identified – the panel mainly relied on evidence from the ASH guidelines for the management of hospitalized medically ill patients, and their expertise
Living Phase – Systematic Reviews

Overall
- Monthly search updates
- Using explicit criteria for updating analyses and publication with new important information

Baseline risk
- Add evidence on prognostic factors
- Search strategy & eligibility criteria may become narrower as quantity and quality of evidence increases
- Use of machine learning to make regular screening manageable

Effect of anticoagulation intensity
- Search strategy & eligibility criteria may focus on RCTs as they become available
- Update analyses with new important data (explicit criteria)
Living Phase – Recommendations

• Continue to work closely with panel and systematic review team
• Reconsider recommendations when important new evidence is identified
• Using explicit criteria for reconsidering recommendations
  • Changes in the evidence of effects (certainty, direction, magnitude)
  • Changes in the evidence for other Evidence-to-Decision domains (cost-effectiveness, equity, others)
• Publish updated recommendations and supporting documents

Timely advice for decision-makers
Living Recommendations


Fig. 2. The main steps of the living guideline process, focused on the unit of update, that is, the living recommendation.
Main Challenges

Evidence

- Large number of citations
- Incomplete reporting
- Risk of bias
- Imprecision
- Evolving field in Living phase

Recommendation formulation process

- Very low certainty evidence
- Not relying on non-COVID-19 evidence
- Criteria to reconsider recommendations with important new evidence in Living phase
- Provide timely and stable guidance
### Case Presentations

<table>
<thead>
<tr>
<th><strong>Patient T</strong></th>
<th><strong>Patient K</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>♂, Chinese, 73 years</td>
<td>♂, Caucasian, 52 years</td>
</tr>
<tr>
<td>BMI 34 kg/m², DM, hypertension</td>
<td>BMI 23 kg/m², Asthma</td>
</tr>
<tr>
<td>COVID-19 day 10</td>
<td>COVID-19 day 6</td>
</tr>
<tr>
<td>High fever, dyspneic at rest</td>
<td>Anosmia, shortness of breath with exercise</td>
</tr>
<tr>
<td>HR 123/min, RR 42/min, Sat 83% at 15L O₂</td>
<td>HR 95/min, RR 20/min, sat 90% at room air</td>
</tr>
</tbody>
</table>

Published October 8, 2020 – New Evidence Available in Blood Advances
Million Dollar Question

What would be the optimal anticoagulant strategy in these 2 patients?
Which ONE of the following options would you suggest for thromboprophylaxis during this medical inpatient’s hospital admission?

A. Subcutaneous low molecular weight heparin (LMWH)
B. Direct oral anticoagulant (Rivaroxaban, or Apixaban)
C. Graduated compression stockings
D. No prophylaxis because patient is low thrombosis risk
COVID-19 coagulopathy: initial reports (China)

Wang D et al, JAMA 2020

Zhou F et al, Lancet 2020
COVID-19 coagulopathy: initial reports (China)

➢ Occurrence of VTE not mentioned

Wang D et al, JAMA 2020
Zhou F et al, Lancet 2020
COVID-19 coagulopathy: initial reports (Europe)

Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis


High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

Julie Helms1,2, Charles Tacquard3, François Severa4, Ian Leonard-Lorant5, Mickael Olhana5, Xavier Delabranche6, Hamid Meriti1,8, Raphaelle Clerc-Jehi3,8, Malika Schenck1, Florence Fayot Gandel1, Samnia Yafi-Kremer4, Vincent Castelain2, Francis Schneider2, Léa Grunebaum5, Eduardo Anglés-Cano2,1, Laurent Setti1,8, Paul-Michel Mentre5,8, Ferhat Meziani4,12 and CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis)

High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients

Jean-François Llitjos1,*, Maxime Leclerc2, Camille Chochois2, Michel Ramakers2, Malika Auvray2, Karim Merouani3

Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy

Corrado Lodigiani1,3, Giacomo Iapichino1, Luca Carena2, Maurizia Coccia1, Paolo Ferrazzi1, Tim Sebastian1, Nila Kucher1, Jan-Dirk Stad1, Clara Sacco1, Bertuzzi Alessia1, Maria Teresa Sandri1, Stefano Barco1,3, on behalf of the Humanitas COVID-19 Task Force
COVID-19 coagulopathy: initial reports (Europe)

➢ Incidence of VTE in ICU 17-70%
COVID-19 coagulopathy: autopsy studies

Macroscopic autopsy findings
A. Patchy aspect of the lung surface (case 1).
B. Cutting surface in (case 4).
C. Pulmonary embolism (case 3).
D. Deep venous thrombosis (case 5).
COVID-19: incidence of VTE

- 9.5% (95%CI 7.5-12)
- 40% (95%CI 27-54)

Nopp S et al, RPTH 2020
Pathophysiology of increased VTE risk

Price LC et al, Eur Respir J 2020
Beneficial non-anticoagulant mechanisms?

- Reduces viral entry to host cells
- Reduces NET formation
- Inhibits heparanase
Intensive anticoagulant therapy beneficial?

- High incidence of VTE
- Beneficial non-anticoagulant mechanisms (?)

- Immunothrombosis
- Overdiagnosis of VTE (?)
## Case 1: COVID-19 Related Critical Illness

**Patient T**

- ♂, Chinese, 73 years
- BMI 34 kg/m², DM, hypertension
- COVID-19 day 10
- High fever, dyspneic at rest
- HR 123/min, RR 42/min, Sat 83% at 15L O₂
Question #1

Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate- or therapeutic-intensity vs. prophylactic-intensity be used for patients with COVID-19 related critical illness who do not have suspected or confirmed VTE?
Which ONE of the following options would you suggest for thromboprophylaxis in a hospitalized patient with COVID-19 related critical illness who does not have suspected or confirmed VTE?

A. Intermediate- or therapeutic-intensity anticoagulation
B. Prophylactic-intensity anticoagulation
C. Graduated compression stockings
D. No prophylaxis because patient is at low thrombosis risk
Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity vs. prophylactic intensity be used for patients with COVID-19 related critical illness who do not have suspected or confirmed VTE?

<table>
<thead>
<tr>
<th>POPULATION:</th>
<th>Patients with COVID-19 related <em>critical illness</em> who do not have suspected or confirmed VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERVENTION:</td>
<td>DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity</td>
</tr>
<tr>
<td>COMPARISON:</td>
<td>Prophylactic-intensity</td>
</tr>
<tr>
<td>MAIN OUTCOMES:</td>
<td>Mortality; Pulmonary embolism; Proximal lower extremity DVT; Venous thromboembolism; Major bleeding; Multiple Organ Failure; Ischemic stroke; Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization; ST-elevation myocardial infarction;</td>
</tr>
</tbody>
</table>
### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Nº of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MORTALITY</strong></td>
<td></td>
<td></td>
<td></td>
<td>Risk with prophylactic intensity</td>
</tr>
<tr>
<td>follow up: range 14 days to 22 days</td>
<td>141 (1 study)</td>
<td>● ● ● ● VERY LOW</td>
<td>OR 0.73 (0.33 to 1.76)</td>
<td>236 per 1,000</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52 fewer per 1,000 (143 fewer to 116 more)</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td></td>
<td></td>
<td></td>
<td>Risk difference with anticoagulation at intermediate or therapeutic-intensity</td>
</tr>
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<td>follow up: range 14 days to 20 days</td>
<td>82 (1 study)</td>
<td>● ● ● ● VERY LOW</td>
<td>OR 0.09 (0.02 to 0.57)</td>
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<td>88 fewer per 1,000 (96 fewer to 40 fewer)</td>
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<tr>
<td><strong>PROXIMAL LOWER EXTREMITY DVT</strong></td>
<td></td>
<td></td>
<td></td>
<td>Risk with prophylactic intensity</td>
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<td>follow up: range 14 days to 20 days</td>
<td>41 (1 study)</td>
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<td></td>
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<td></td>
<td>66 fewer per 1,000 (99 fewer to 87 more)</td>
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<tr>
<td><strong>VTE (DVT or PE)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Risk difference with anticoagulation at intermediate or therapeutic-intensity</td>
</tr>
<tr>
<td>follow up: range 18 days to 28 days</td>
<td>118 (2 studies)</td>
<td>● ● ● ● VERY LOW</td>
<td>OR 0.87 (0.45 to 1.67)</td>
<td>130 per 1,000</td>
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<td></td>
<td>15 fewer per 1,000 (67 fewer to 70 more)</td>
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<td><strong>MAJOR BLEEDING</strong></td>
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<td>follow up: mean 16 days</td>
<td>141 (1 study)</td>
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<td>OR 3.84 (1.44 to 10.21)</td>
<td>84 per 1,000</td>
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<td>176 more per 1,000 (33 more to 400 more)</td>
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Recommendation

The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation in patients with COVID-19 related critical illness who do not have suspected or confirmed VTE (Conditional recommendation based on very low certainty in the evidence about effects).

The panel agreed that there was less uncertainty regarding the influence on undesirable effects (bleeding) compared with desirable effects (mortality and VTE). This was driven by extensive indirect evidence of dose-dependent effects of anticoagulation on bleeding.

- Individualized assessment
- No validated risk assessment models for in patients with COVID-19
- No direct high-quality evidence comparing different anticoagulants
Case 2: COVID-19 related acute illness

Patient K

♂, Caucasian, 52 years
BMI 23 kg/m², Asthma
COVID-19 day 6
Anosmia, shortness of breath with exercise
HR 95/min, RR 20/min, sat 90% at room air
Question #2

Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity vs. prophylactic-intensity be used for patients with COVID-19 related acute illness who do not have suspected or confirmed VTE?
Which ONE of the following options would you suggest for thromboprophylaxis in a hospitalized patient with COVID-19 related acute illness who does not have suspected or confirmed VTE?

A. Intermediate- or therapeutic-intensity anticoagulation
B. Prophylactic-intensity anticoagulation
C. Graduated compression stockings
D. No prophylaxis because patient is at low thrombosis risk
Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity vs. prophylactic-intensity be used for patients with COVID-19 related acute illness who do not have suspected or confirmed VTE?

**POPULATION:** Patients with COVID-19 related *acute illness* who do not have suspected or confirmed VTE

**INTERVENTION:** DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity

**COMPARISON:** Prophylactic-intensity

**MAIN OUTCOMES:** All-cause mortality; Pulmonary embolism; Proximal lower extremity DVT; Venous thromboembolism; Major bleeding; Multiple organ failure; Ischemic stroke; Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization; ST-elevation myocardial infarction;
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<th>Relative effect (95% CI)</th>
<th>Risk with prophylactic-intensity</th>
<th>Risk difference with anticoagulation at intermediate- or therapeutic-intensity</th>
</tr>
</thead>
<tbody>
<tr>
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The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation in 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)

The panel agreed that there was less uncertainty regarding the influence on undesirable effects (bleeding) compared with desirable effects (mortality and VTE). This was driven by extensive indirect evidence of dose-dependent effects of anticoagulation on bleeding.

- Individualized assessment
- No validated risk assessment models for in patients with COVID-19
- No direct high-quality evidence comparing different anticoagulants
Very low certainty of evidence

**Baseline risk studies**
- Lack of definitions and/or descriptions of outcome measurement
- Incomplete/missing follow-up
- Incidence rates not reported (i.e. events per unit of follow-up)

**Effect of anticoagulation studies**
- Confounding with use of higher intensities in selected patients
- Lack of details regarding reported anticoagulant intensities
In Summary: Back to our Objectives

1. Describe VTE prophylaxis recommendations for hospitalized patients with COVID-19 related **critical illness** who do not have suspected or confirmed VTE
   - Intermediate- or therapeutic-intensity versus prophylactic intensity anticoagulation

2. Describe VTE prophylaxis recommendations for hospitalized patients with COVID-19 related **acute illness** who do not have suspected or confirmed VTE
   - Intermediate- or therapeutic-intensity versus prophylactic intensity anticoagulation
Acknowledgements

• ASH Guideline Panel team members
• Knowledge Synthesis team members
• McMaster University GRADE Centre
• Author of ASH VTE Slide Sets: Erik Klok, MD, PhD, Deborah Siegal, MD, MSc, Robby Nieuwlaat, PhD, MSc, Adam Cuker, MD, MS

See more about the ASH VTE guidelines at www.hematology.org/COVIDguidelines