



# 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

**Slide set authors:**

Erik Klok, MD, PhD, Leiden University Medical Center

Deborah Siegal, MD, MSc, University of Ottawa

Robby Nieuwlaat, PhD, MSc, McMaster University

Adam Cuker, MD, MS, University of Pennsylvania



# Clinical Guidelines

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

Adam Cuker, Eric K. Tseng, Robby Nieuwlaat, Pantep Angchaisuksiri, Clifton Blair, Kathryn Dane, Jennifer Davila, Maria T. DeSancho, David Diuguid, Daniel O. Griffin, Susan R. Kahn, Frederikus A. Klok, Alfred Ian Lee, Ignacio Neumann, Ashok Pai, Menaka Pai, Marc Righini, Kristen M. Sanfilippo, Deborah Siegal, Mike Skara, Kamshad Touri, Elie A. Akl, Imad Bou Akl, Mary Boulos, Romina Brignardello-Petersen, Rana Charide, Matthew Chan, Karin Dearness, Andrea J. Darzi, Philipp Kolb, Luis E. Colunga-Lozano, Razan Mansour, Gian Paolo Morgano, Rami Z. Morsi, Atefeh Noori, Thomas Piggott, Yuan Qiu, Yetiani Roldan, Finn Schunemann, Adrienne Stevens, Karla Solo, Matthew Ventresca, Wojtek Wiercioch, Reem A. Mustafa, Holger J. Schunemann

CLINICAL GUIDELINES

American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19

Adam Cuker,<sup>1</sup> Eric K. Tseng,<sup>2,4</sup> Robby Nieuwlaat,<sup>5,6</sup> Pantep Angchaisuksiri,<sup>7</sup> Clifton Blair,<sup>7</sup> Kathryn Dane,<sup>8</sup> Jennifer Davila,<sup>9</sup> Maria T. DeSancho,<sup>10</sup> David Diuguid,<sup>11</sup> Daniel O. Griffin,<sup>12,13</sup> Susan R. Kahn,<sup>14</sup> Frederikus A. Klok,<sup>15</sup> Alfred Ian Lee,<sup>16</sup> Ignacio Neumann,<sup>17</sup> Ashok Pai,<sup>18</sup> Menaka Pai,<sup>19</sup> Marc Righini,<sup>20</sup> Kristen M. Sanfilippo,<sup>21</sup> Deborah Siegal,<sup>22,23</sup> Mike Skara,<sup>24</sup> Kamshad Touri,<sup>25</sup> Elie A. Akl,<sup>26</sup> Imad Bou Akl,<sup>27</sup> Mary Boulos,<sup>28</sup> Romina Brignardello-Petersen,<sup>29</sup> Rana Charide,<sup>30</sup> Matthew Chan,<sup>31</sup> Karin Dearness,<sup>32</sup> Andrea J. Darzi,<sup>33</sup> Philipp Kolb,<sup>34</sup> Luis E. Colunga-Lozano,<sup>35</sup> Razan Mansour,<sup>36</sup> Gian Paolo Morgano,<sup>37,38</sup> Rami Z. Morsi,<sup>39</sup> Atefeh Noori,<sup>40,41</sup> Thomas Piggott,<sup>42</sup> Yuan Qiu,<sup>43</sup> Yetiani Roldan,<sup>44</sup> Finn Schunemann,<sup>45</sup> Adrienne Stevens,<sup>46</sup> Karla Solo,<sup>47</sup> Matthew Ventresca,<sup>48</sup> Wojtek Wiercioch,<sup>49</sup> Reem A. Mustafa,<sup>50,51</sup> and Holger J. Schunemann,<sup>52,53,54</sup>

<sup>1</sup>Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; <sup>2</sup>St. Michael's Hospital, Division of Hematology/Oncology, University of Toronto, Toronto, ON, Canada; <sup>3</sup>Michael G. DeGroote Cochrane Canada Centre, GRADE Centre, and <sup>4</sup>Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; <sup>5</sup>Division of Hematology, Department of Medicine, Ramathongkosi Hospital, Mahidol University, Bangkok, Thailand; <sup>6</sup>Union, NJ; <sup>7</sup>Department of Pharmacy, The Johns Hopkins Hospital, Baltimore, MD; <sup>8</sup>Children's Hospital at Montefiore, Division of Pediatric Hematology, Oncology, and Cellular Therapies, Albert Einstein College of Medicine, Bronx, NY; <sup>9</sup>Division of Hematology/Oncology, Department of Medicine, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY; <sup>10</sup>Department of Medicine, College of Physicians and Surgeons and <sup>11</sup>Division of Infectious Diseases, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY; <sup>12</sup>Research and Development of United Health Group, Minnesota, MN; <sup>13</sup>PhysHealth, NY, Lake Success, NY; <sup>14</sup>Department of Medicine, McGill University, Montreal, QC, Canada; <sup>15</sup>Thrombosis and Hemostasis, Department of Medicine, Leiden University Medical Center, Leiden, The Netherlands; <sup>16</sup>Section of Hematology, School of Medicine, Yale University, New Haven, CT; <sup>17</sup>Department of Internal Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile; <sup>18</sup>Division of Hematology and Oncology, Kaiser Permanente, Oakland/Berkeley, CA; <sup>19</sup>Department of Medicine, McMaster University, Hamilton, ON, Canada; <sup>20</sup>Division of Angiology and Hemostasis, Faculty of Medicine, Geneva University Hospitals, University of Geneva, Geneva, Switzerland; <sup>21</sup>Department of Medicine, Washington University School of Medicine St. Louis, St. Louis, MO; <sup>22</sup>Department of Medicine and <sup>23</sup>Ontario Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; <sup>24</sup>College Grove, MN; <sup>25</sup>Toronto, ON, Canada; <sup>26</sup>Department of Internal Medicine, American University of Beirut, Beirut, Lebanon; <sup>27</sup>Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada; <sup>28</sup>Clinical Research Institute, American University of Beirut, Beirut, Lebanon; <sup>29</sup>Library Services, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada; <sup>30</sup>Department of Clinical Medicine, Health Science Center, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico; <sup>31</sup>Office of Scientific Affairs and Research, King Hussein Cancer Center, Amman, Jordan; <sup>32</sup>Department of Neurology, University of Chicago, Chicago, IL; <sup>33</sup>The Michael G. DeGroote National Pain Center, McMaster University, Hamilton, ON, Canada; <sup>34</sup>Medizinische Fakultät, Albert-Ludwigs-Universität Freiburg, Freiburg, Germany; <sup>35</sup>Department of Internal Medicine, Division of Nephrology, University of Kansas Medical Center, Kansas City, KS; and <sup>36</sup>Institute for Evidence in Medicine, Medical Center/Faculty of Medicine, University of Freiburg, Freiburg, Germany

**Background:** Coronavirus disease 2019 (COVID-19)-related critical illness and acute illness are associated with a risk of venous thromboembolism (VTE).  
**Objective:** These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in decisions about the use of anticoagulation for thromboprophylaxis for patients with COVID-19-related critical illness and acute illness who do not have confirmed or suspected VTE.  
**Methods:** ASH formed a multidisciplinary guideline panel and applied strict management strategies to minimize potential bias from conflicts of interest. The panel included 3 patient representatives. The McMaster University GRADE Centre supported the guideline-development process, including performing systematic evidence reviews (up to 19 August 2020). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subject to public comment.  
**Results:** The panel agreed on 2 recommendations. The panel issued conditional recommendations in favor of prophylactic-intensity anticoagulation over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19-related critical illness or acute illness who do not have confirmed or suspected VTE.  
**Conclusions:** Those recommendations were based on very low certainty in the evidence, underscoring the need for high-quality, randomized controlled trials comparing different intensities of anticoagulation. They will be updated using a living recommendation approach as new evidence becomes available.

Submitted 3 November 2020; accepted 18 December 2020; published online XXX. The full-text version of this article contains a data supplement.  
 DOI 10.1182/bloodadvances.2020099768 © 2021 by The American Society of Hematology  
 \*A.C. and E.K.T. are joint first authors.

2021 • VOLUME 6, NUMBER 0



## 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?

### PANEL FORMATION

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

### CLINICAL QUESTIONS

2 **clinically-relevant questions** generated in **PICO format** (population, intervention, comparison, outcome)

#### 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?”*

### EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

### MAKING RECOMMENDATIONS

- **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.



## How patients and clinicians should use these recommendations

	<b>STRONG Recommendation</b> ("The panel recommends...")	<b>CONDITIONAL Recommendation</b> ("The panel suggests...")
<b>For patients</b>	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
<b>For clinicians</b>	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use <b>shared decision making</b> .



## 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

# GRADEpro

**Formulate question**

**Assess single studies**

**PICO**

- 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**

Outcomes	Plain language statements	Absolute Effect	Relative effect	Certainty of the evidence
Breast cancer mortality (short case survival) for women aged 40 to 44	Screening probably reduces breast cancer-related deaths slightly.	400 (95% CI 341 to 459) per 10000 patients	RR 0.89 (0.79 to 1.00)	MODERATE
Breast cancer mortality (longest case survival) for women aged 40 to 44	Screening probably reduces breast cancer-related deaths slightly.	480 (95% CI 411 to 549) per 10000 patients	RR 0.92 (0.81 to 1.03)	MODERATE

**Evidence to decision or recommendation framework**

Criteria	Research evidence	Additional considerations	Panel's judgments
Benefits & harms of the options	●	●	●●●●
Values & balance of effects	●	●	●●●●
Resources required	●	●	●●●●
Cost effectiveness	●	●	●●●●
Equity	●	●	●●●●
Acceptability	●	●	●●●●
Feasibility	●	●	●●●●

**Grade recommendations (Evidence to Recommendation)**

- For or against (direction)
- Strong or conditional/weak (strength)

**Panel**

**Recommendation/Decision Guideline/coverage decision**

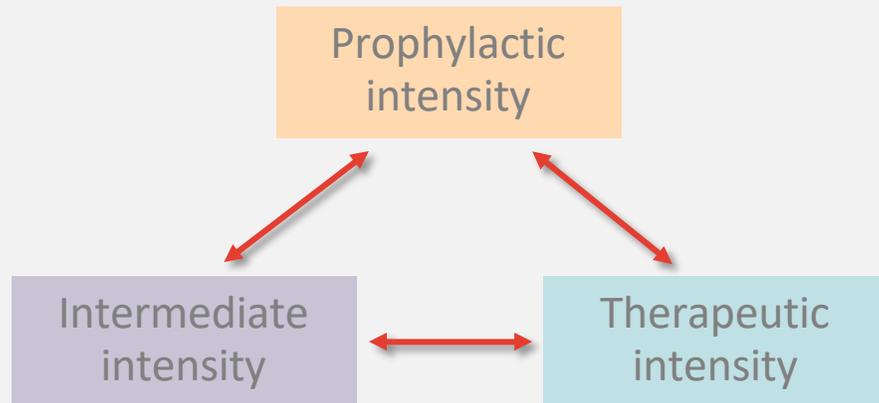
American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

**Evidence synthesis (systematic review/HTA)**

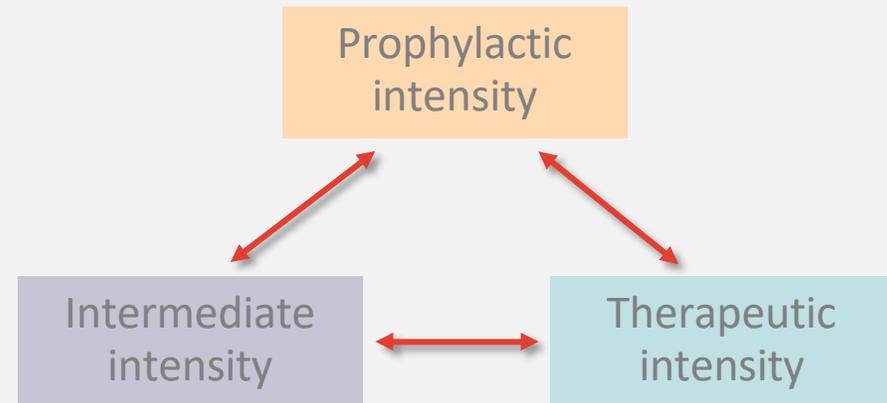
## PICO Question Generation & Prioritization

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

### Critically ill COVID-19



### Acutely ill COVID-19





## 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/>

### 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	Initial confidence in an estimate of effect
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	▲ Higher if*
<b>Risk of Bias</b>	Large effect
<b>Inconsistency</b>	Dose Response
<b>Indirectness</b>	All plausible confounding & bias
<b>Imprecision</b>	• Would reduce a demonstrated effect
<b>Publication bias</b>	• or • Would suggest spurious effect if no effect was observed

### 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)

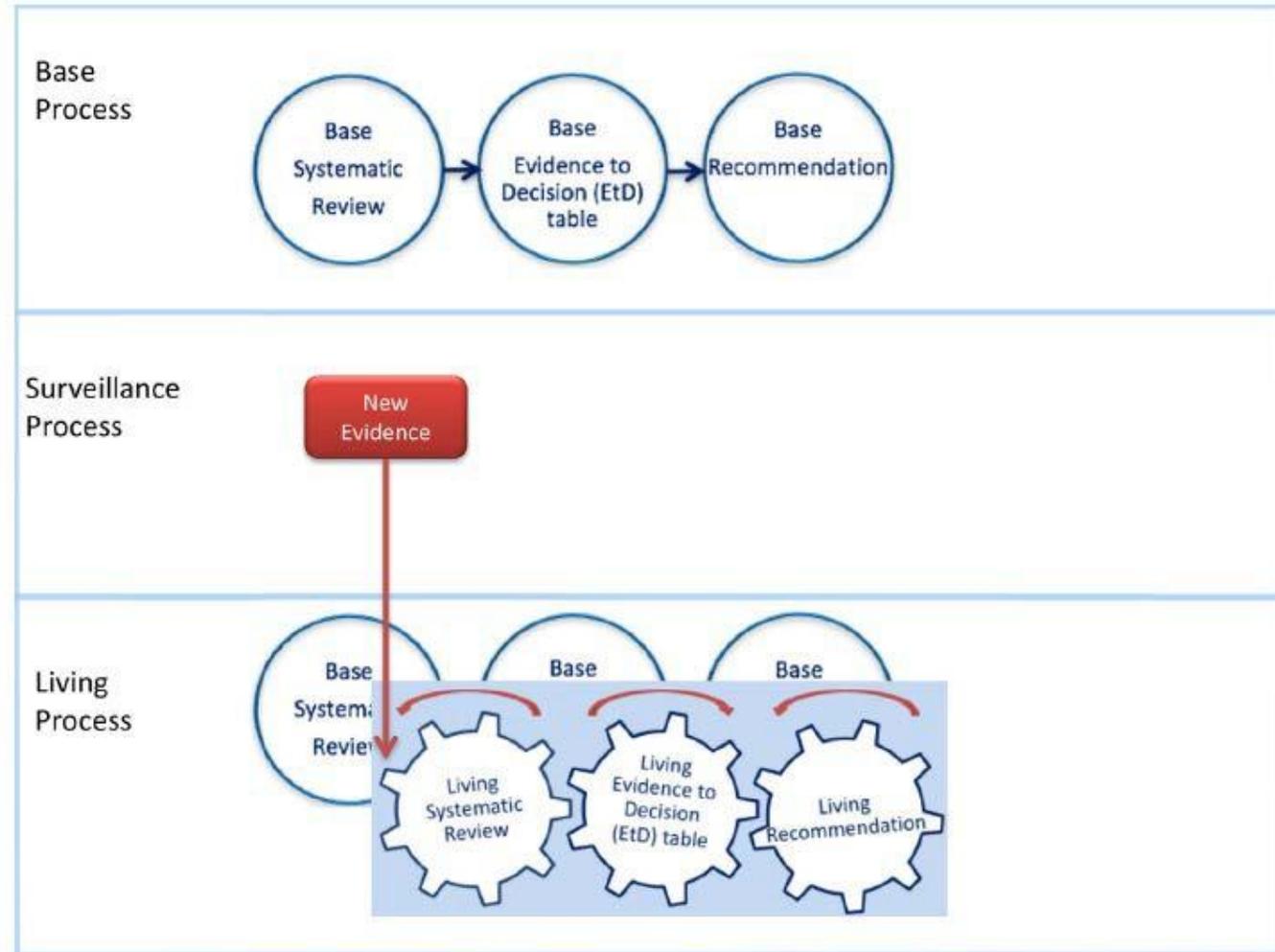


## Living Phase – Recommendations

- 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.

Akl EA, et al. Living systematic reviews: 4. Living guideline recommendations. *J Clin Epidemiol.* 2017;91:47-53.



## 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

### Patient T

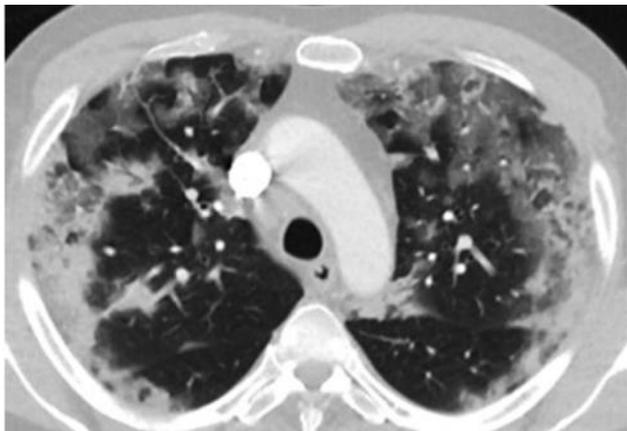
♂, Chinese, 73 years

BMI 34 kg/m<sup>2</sup>, DM, hypertension

COVID-19 day 10

High fever, dyspneic at rest

HR 123/min, RR 42/min, Sat 83% at 15L O<sub>2</sub>



### Patient K

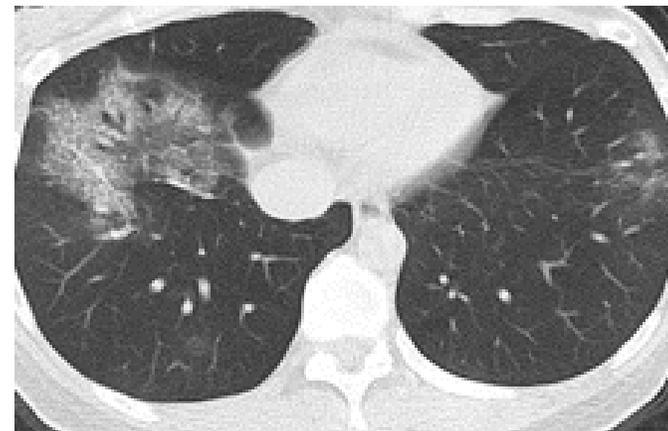
♂, Caucasian, 52 years

BMI 23 kg/m<sup>2</sup>, Asthma

COVID-19 day 6

Anosmia, shortness of breath with exercise

HR 95/min, RR 20/min, sat 90% at room air





## Million Dollar Question

What would be the optimal anticoagulant strategy in these 2 patients?

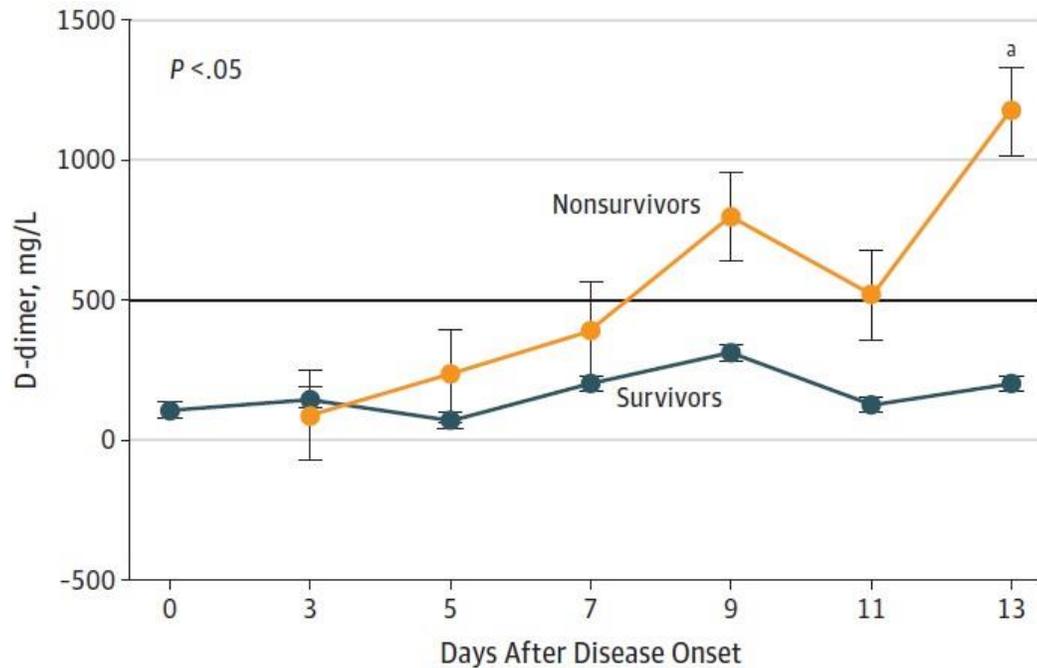


Which ONE of the following options would you suggest for thromboprophylaxis during this medical inpatient's hospital admission?

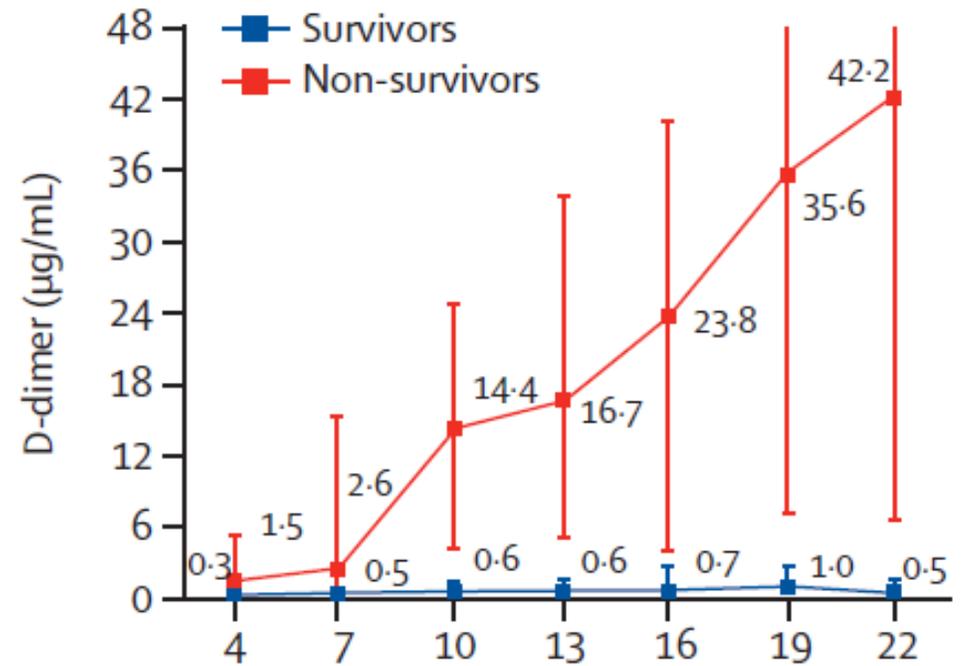
- A. Subcutaneous low molecular weight heparin (LMWH)
- B. Direct oral anticoagulant (Rivaroxaban, or Apixaban)
- C. Graduated compression stockings
- D. No prophylaxis because patient is low thrombosis risk



## COVID-19 coagulopathy: initial reports (China)

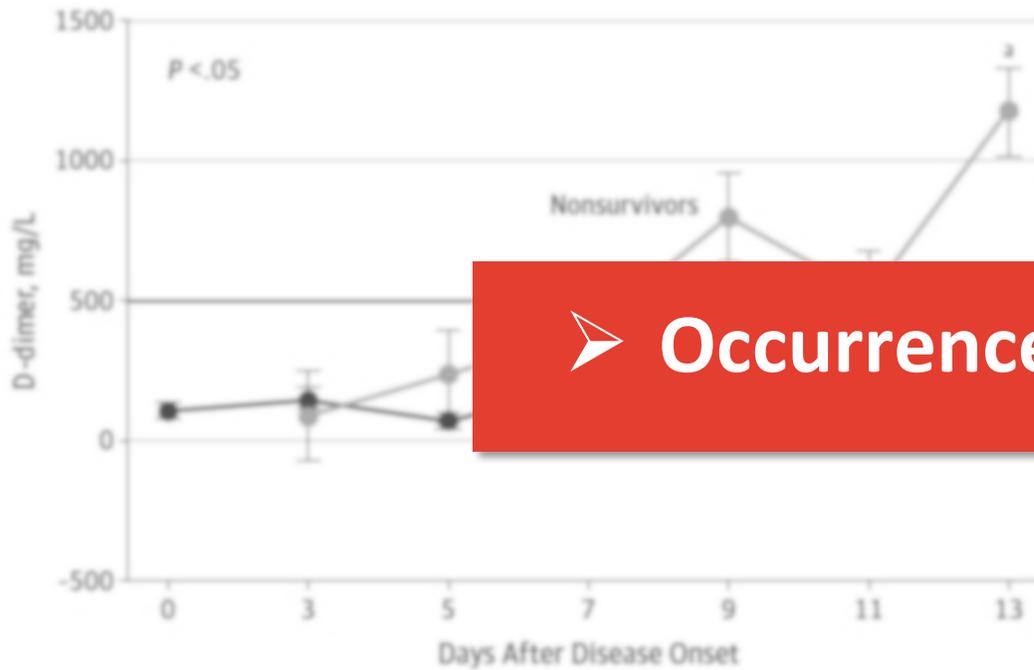


Wang D *et al*, JAMA 2020

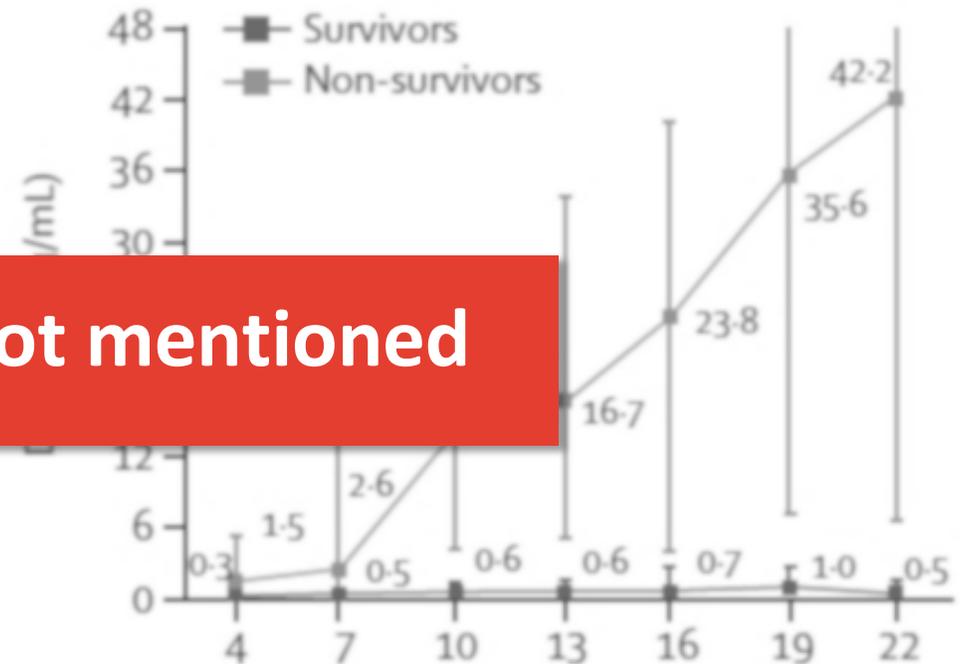


Zhou F *et al*, Lancet 2020

## COVID-19 coagulopathy: initial reports (China)



Wang D *et al*, JAMA 2020



Zhou F *et al*, Lancet 2020



# COVID-19 coagulopathy: initial reports (Europe)

Thrombosis Research 191 (2020) 148–150

Contents lists available at ScienceDirect

**Thrombosis Research**

journal homepage: [www.elsevier.com/locate/thromres](http://www.elsevier.com/locate/thromres)

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

F.A. Klok<sup>a,\*</sup>, M.J.H.A. Kruip<sup>b</sup>, N.J.M. van der Meer<sup>c,d</sup>, M.S. Arbus<sup>e</sup>, D. Gommers<sup>f</sup>, K.M. Kant<sup>g</sup>, F.H.J. Kaptein<sup>a</sup>, J. van Paassen<sup>e</sup>, M.A.M. Stals<sup>a</sup>, M.V. Huisman<sup>a,1</sup>, H. Endeman<sup>f,1</sup>

**BRIEF REPORT**

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

Jean-François Llitjos<sup>1</sup> | Maxime Leclerc<sup>2</sup> | Camille Chochois<sup>2</sup> | Jean-Michel Monsallier<sup>3</sup> | Michel Ramakers<sup>2</sup> | Malika Auvray<sup>2</sup> | Karim Merouani<sup>3</sup>

Intensive Care Med  
<https://doi.org/10.1007/s00134-020-06062-x>

**ORIGINAL**

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

Julie Helms<sup>1,2</sup>, Charles Tacquard<sup>3</sup>, François Severac<sup>4</sup>, Ian Leonard-Lorant<sup>5</sup>, Mickaël Ohana<sup>5</sup>, Xavier Delabranche<sup>3</sup>, Hamid Merdji<sup>1,6</sup>, Raphaël Clere-Jehl<sup>1,2</sup>, Malika Schenck<sup>7</sup>, Florence Fagot Gandet<sup>7</sup>, Samira Fafi-Kremer<sup>2,8</sup>, Vincent Castelain<sup>7</sup>, Francis Schneider<sup>7</sup>, Lélia Grunebaum<sup>9</sup>, Eduardo Anglés-Cano<sup>10</sup>, Laurent Sattler<sup>9</sup>, Paul-Michel Mertes<sup>3</sup>, Ferhat Meziani<sup>1,6\*</sup> and CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis)

Thrombosis Research 191 (2020) 9–14

Contents lists available at ScienceDirect

**Thrombosis Research**

journal homepage: [www.elsevier.com/locate/thromres](http://www.elsevier.com/locate/thromres)

Full Length Article

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

Corrado Lodigiani<sup>a,b,\*</sup>, Giacomo Iapichino<sup>c</sup>, Luca Carenzo<sup>c</sup>, Maurizio Cecconi<sup>b,c</sup>, Paola Ferrazzi<sup>a</sup>, Tim Sebastian<sup>d</sup>, Nils Kucher<sup>d</sup>, Jan-Dirk Studt<sup>e</sup>, Clara Sacco<sup>a</sup>, Bertuzzi Alexia<sup>f</sup>, Maria Teresa Sandri<sup>a</sup>, Stefano Barco<sup>d,h</sup>, on behalf of the Humanitas COVID-19 Task Force



# COVID-19 coagulopathy: initial reports (Europe)



Intensive Care Med  
https://doi.org/10.1007/s00134-020-06062-x

## ORIGINAL

### High risk of thrombosis in patients with COVID-19: a multicenter study

Confirmation of the high risk of thrombosis in critically ill ICU patients with COVID-19  
F.A. Klok<sup>1,2</sup>, M.J.H.A. Kruijs<sup>1</sup>, M. van der Sluis<sup>1</sup>, F.H.J. Kaptein<sup>1</sup>, J. van Paassen<sup>1</sup>

➤ Incidence of VTE in ICU 17-70%

Mickael Ohana<sup>3</sup>, Xavier Delabranche<sup>4</sup>, Fabrice Gandet<sup>5</sup>, Samira Fafi-Kremer<sup>2,6</sup>, Gilles-Cano<sup>7,8</sup>, Laurent Sattler<sup>9</sup>, Valérie Michel-Merles<sup>10</sup>, Ferhat Meziane<sup>11</sup> and CRICS-TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis)

## BRIEF REPORT



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

Jean-François Llitjos<sup>1</sup> | Maxime Leclerc<sup>2</sup> | Camille Chochois<sup>2</sup> | Jean-Michel Monsallier<sup>3</sup> | Michel Ramakers<sup>2</sup> | Malika Auvray<sup>2</sup> | Karim Merouani<sup>3</sup>



## Full Length Article

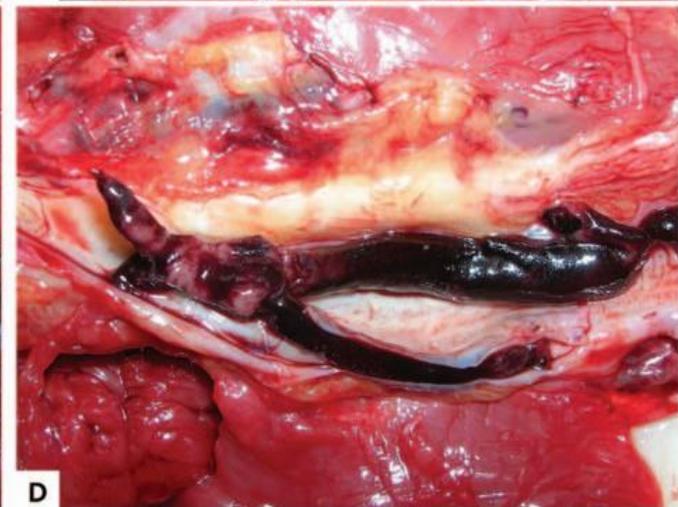
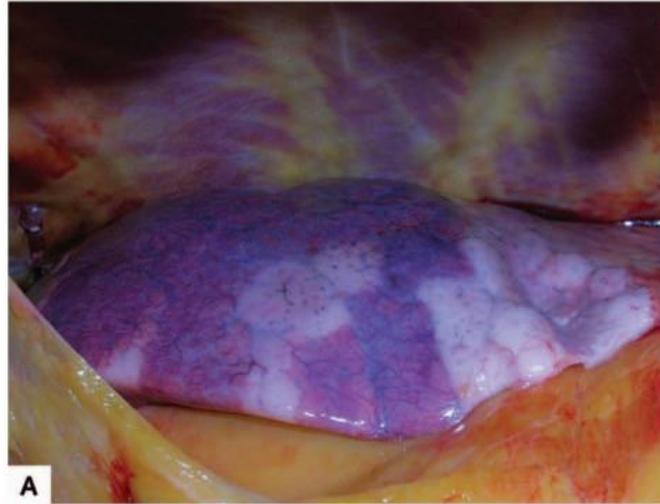
### Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy

Corrado Lodigiani<sup>1,2,3</sup>, Giacomo Iapichino<sup>4</sup>, Luca Carenzo<sup>5</sup>, Maurizio Cecconi<sup>6,7</sup>, Paola Ferrazzi<sup>8</sup>, Tim Sebastian<sup>9</sup>, Nils Kucher<sup>10</sup>, Jan-Dirk Studt<sup>11</sup>, Clara Sacco<sup>12</sup>, Bertuzzi Alexia<sup>13</sup>, Maria Teresa Sandri<sup>14</sup>, Stefano Barco<sup>15</sup>, on behalf of the Humanitas COVID-19 Task Force

## 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).

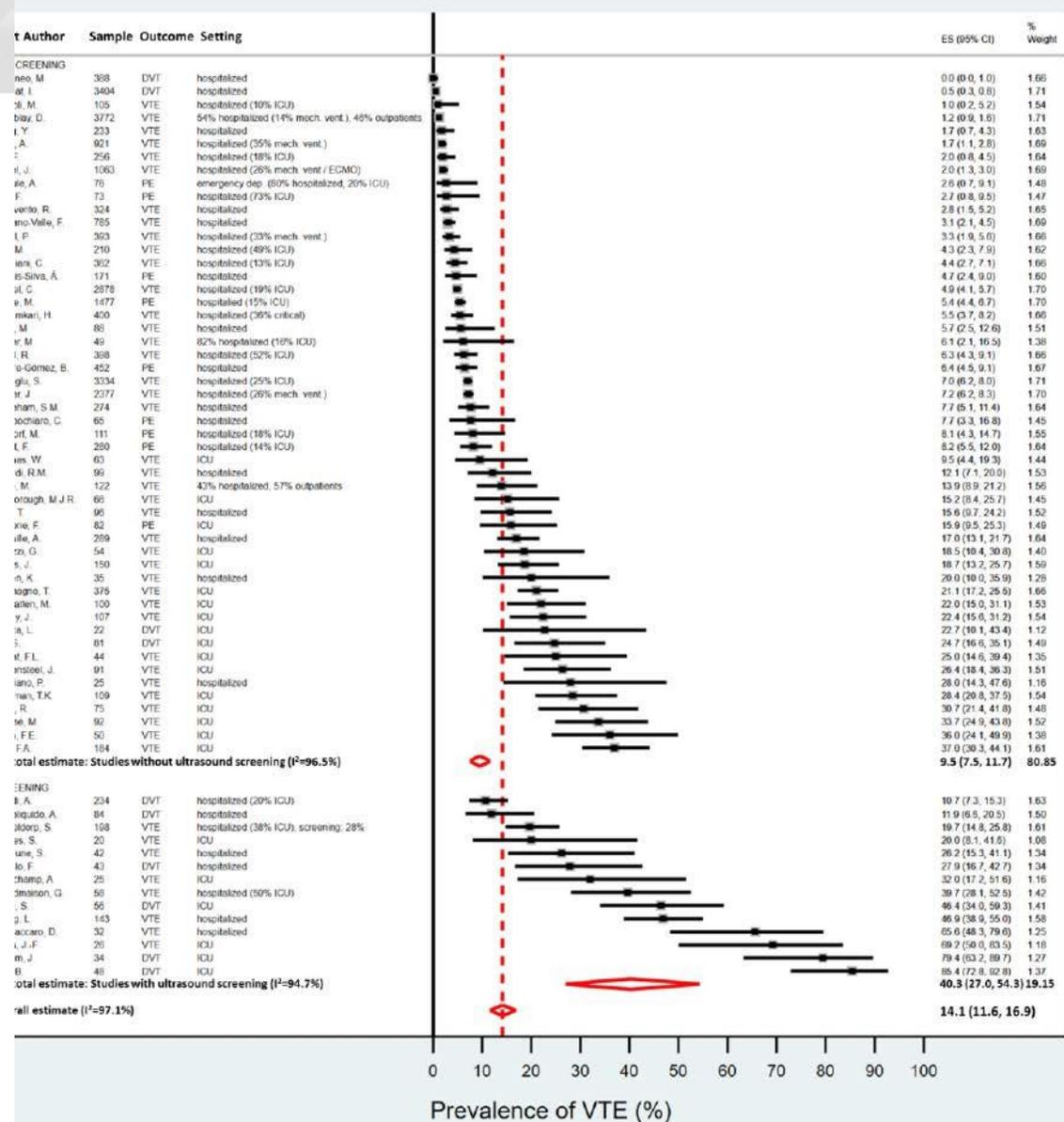




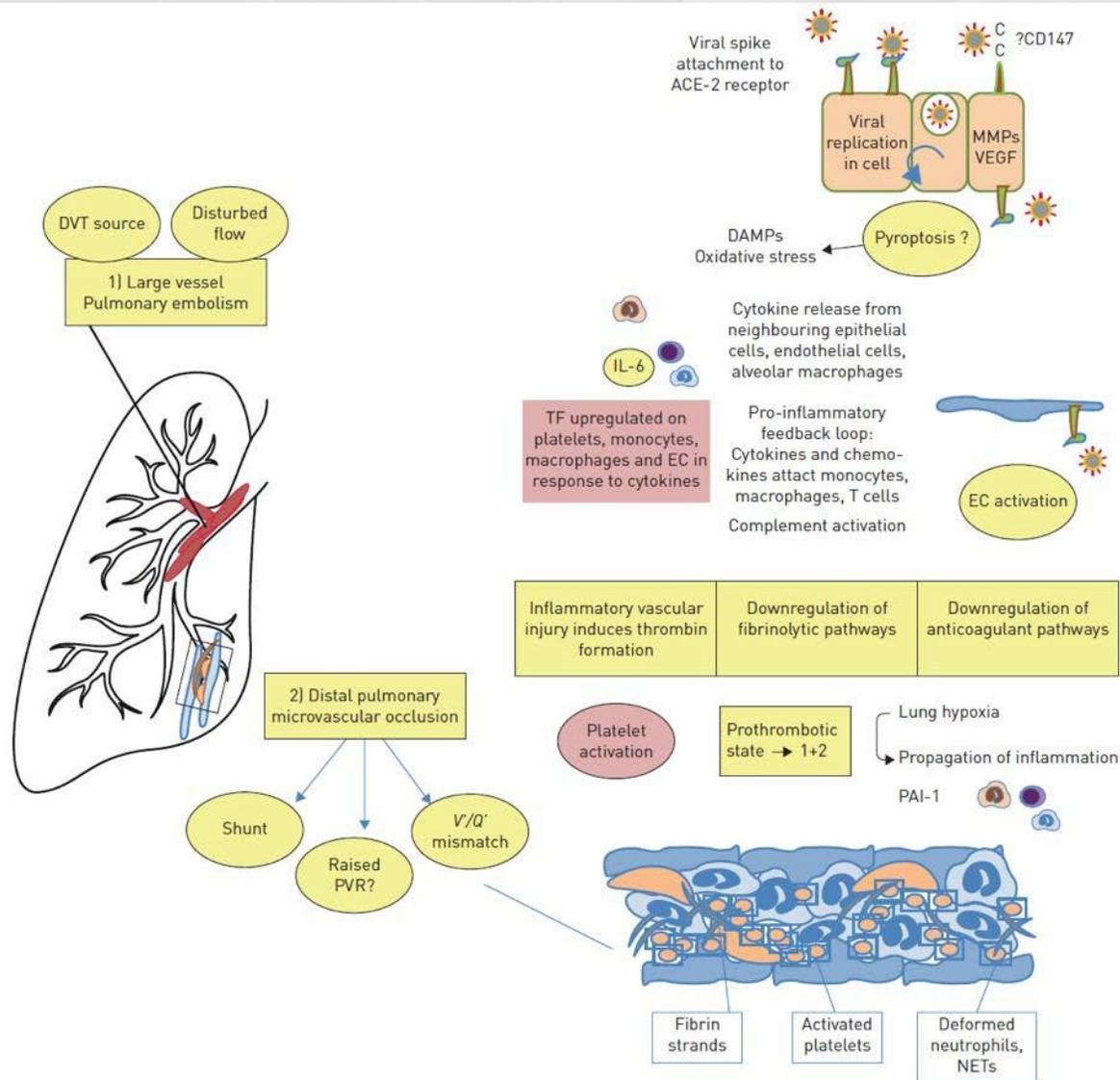
# COVID-19: incidence of VTE

➤ 9.5% (95%CI 7.5-12)

➤ 40% (95%CI 27-54)



# Pathophysiology of increased VTE risk



## 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

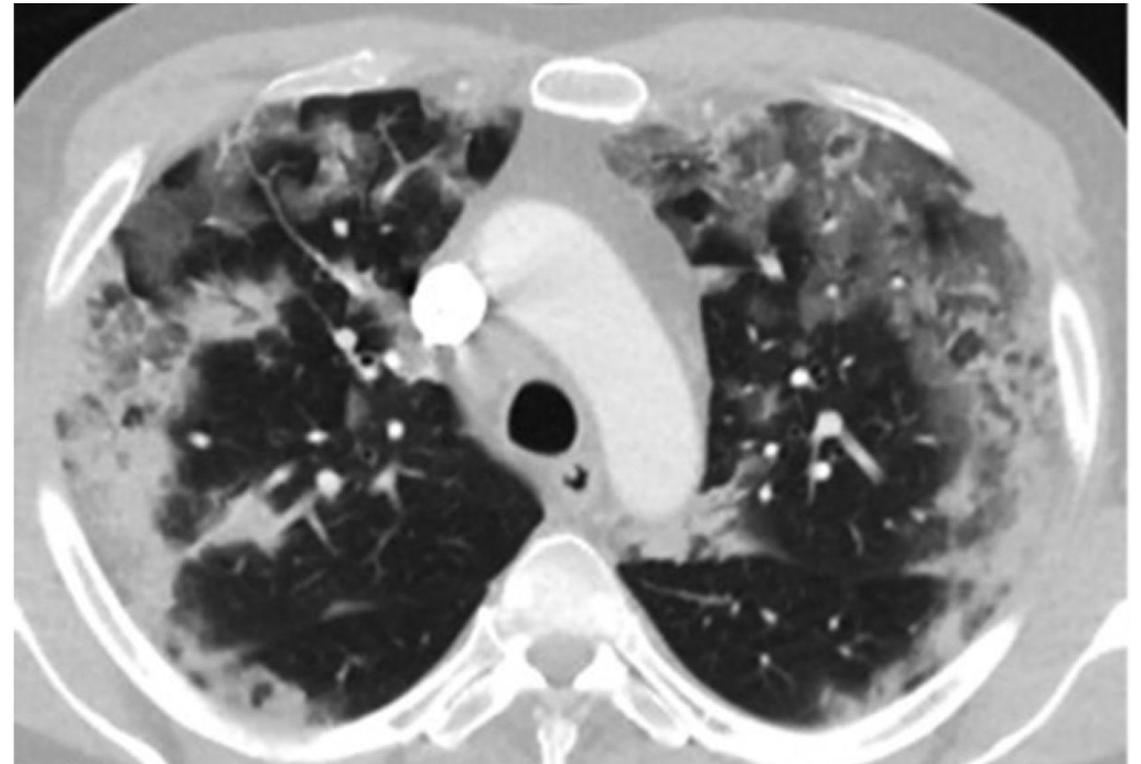
♂, Chinese, 73 years

BMI 34 kg/m<sup>2</sup>, DM, hypertension

COVID-19 day 10

High fever, dyspneic at rest

HR 123/min, RR 42/min, Sat 83% at 15L O<sub>2</sub>





## 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?

<b>POPULATION:</b>	Patients with COVID-19 related <i>critical illness</i> who do not have suspected or confirmed VTE
<b>INTERVENTION:</b>	DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity
<b>COMPARISON:</b>	Prophylactic-intensity
<b>MAIN OUTCOMES:</b>	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;

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with prophylactic intensity	Risk difference with anticoagulation at intermediate or therapeutic-intensity
<b>MORTALITY</b> follow up: range 14 days to 22 days	141 (1 study)	● ● ● ● VERY LOW	OR 0.73 (0.33 to 1.76)	236 per 1,000	52 fewer per 1,000 (143 fewer to 116 more)
<b>PE</b> follow up: range 14 days to 20 days	82 (1 study)	● ● ● ● VERY LOW	OR 0.09 (0.02 to 0.57)	98 per 1,000	88 fewer per 1,000 (96 fewer to 40 fewer)
<b>PROXIMAL LOWER EXTREMITY DVT</b> follow up: range 14 days to 20 days	41 (1 study)	● ● ● ● VERY LOW	OR 0.35 (0.06 to 2.02)	106 per 1,000	66 fewer per 1,000 (99 fewer to 87 more)
<b>VTE (DVT or PE)</b> follow up: range 18 days to 28 days	118 (2 studies)	● ● ● ● VERY LOW	OR 0.87 (0.45 to 1.67)	130 per 1,000	15 fewer per 1,000 (67 fewer to 70 more)
<b>MAJOR BLEEDING</b> follow up: mean 16 days	141 (1 study)	● ● ● ● VERY LOW	OR 3.84 (1.44 to 10.21)	84 per 1,000	176 more per 1,000 (33 more to 400 more)

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
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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

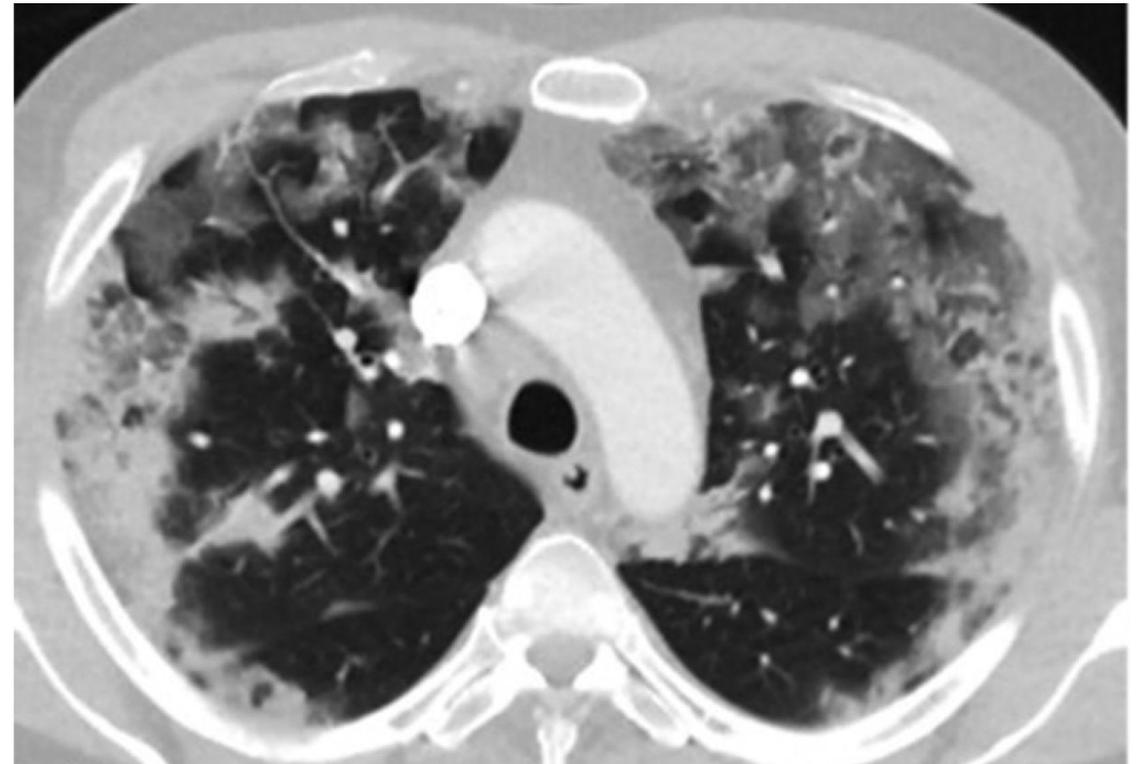
♂, Caucasian, 52 years

BMI 23 kg/m<sup>2</sup>, 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?

<b>POPULATION:</b>	Patients with COVID-19 related <i>acute illness</i> who do not have suspected or confirmed VTE
<b>INTERVENTION:</b>	DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity
<b>COMPARISON:</b>	Prophylactic-intensity
<b>MAIN OUTCOMES:</b>	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;

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with prophylactic-intensity	Risk difference with anticoagulation at intermediate- or therapeutic-intensity
<b>ALL-CAUSE MORTALITY</b> follow up: 14 days	2626 (1 study)	● ● ● ● VERY LOW	HR 0.86 (0.73 to 1.02)	148 per 1,000	19 fewer per 1,000 (38 fewer to 3 more)
<b>PE</b> follow up: range 4 days to 28 days	82 (1 study)	● ● ● ● VERY LOW	OR 0.09 (0.02 to 0.57)	16 per 1,000	15 fewer per 1,000 (16 fewer to 7 fewer)
<b>PROXIMAL LOWER EXTREMITY DVT</b> follow up: 28 days	41 (1 study)	● ● ● ● VERY LOW	OR 0.35 (0.06 to 2.02)	20 per 1,000	13 fewer per 1,000 (18 fewer to 19 more)
<b>VTE</b> follow up: range 6 days to 28 days	0 (1 study)	-	-	Baseline (2 studies, range 2.0% to 3.1%); 0/19 (0%) on therapeutic (other indications) vs. 39/179 (22%) on proph/intermediate (1 study).	
<b>MAJOR BLEEDING</b> follow up: 14 days	0 (2 studies)	● ● ● ● VERY LOW	-	Pooled baseline risk of 1.7% (5 studies); Follow-up 4 to 12 days: lowest OR 1.42 and highest adjusted HR 3.89 (7 more to 46 more major bleeds per 1000 patients)	

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
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- 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](http://www.hematology.org/COVIDguidelines)