



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

blood advances

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

Adam Cuker,^{1,4} Eric K. Tseng,^{2,4} Robby Nieuwlaat,^{2,5} Pantep Angchaisuksiri,⁶ Clifton Blair,⁷ Kathryn Dane,⁸ Jennifer Davila,⁹ Maria T. DeSancho,¹⁰ David Diuguid,¹¹ Daniel O. Griffin,^{12,14} Susan R. Kahn,¹⁵ Frederikus A. Klok,¹⁶ Alfred Ian Lee,¹⁷ Ignacio Neumann,¹⁸ Ashok Pai,¹⁹ Menaka Pai,²⁰ Marc Righini,²¹ Kristen M. Sanfilippo,²² Deborah Siegal,^{23,24} Mike Skara,²⁵ Kamshad Touri,²⁶ Elie A. Akl,²⁷ Imad Bou Akl,²⁷ Mary Boulos,²⁸ Romina Brignardello-Petersen,⁹ Rana Charide,²⁹ Matthew Chan,³⁰ Karin Dearness,³⁰ Andrea J. Darzi,³⁰ Philipp Kolb,²⁸ Luis E. Colunga-Lozano,³¹ Razan Mansour,³² Gian Paolo Morgano,³³ Rami Z. Morsi,³³ Atefeh Noori,^{34,34} Thomas Piggott,³ Yuan Qiu,³⁵ Yetiani Roldan,³ Finn Schunemann,³⁶ Adrienne Stevens,^{3,5} Karla Solo,^{3,5} Matthew Ventresca,^{3,5} Wojtek Wiercioch,^{3,5} Reem A. Mustafa,^{3,5,36} and Holger J. Schunemann^{3,5,20,37}

¹Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; ²St. Michael's Hospital, Division of Hematology/Oncology, University of Toronto, Toronto, ON, Canada; ³Michael G. DeGroote Cochrane Canada Centre, ⁴McGRADE Centre, and ⁵Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; ⁶Division of Hematology, Department of Medicine, Ramathub Hospital, Mahidol University, Bangkok, Thailand; ⁷Union, NJ; ⁸Department of Pharmacy, The Johns Hopkins Hospital, Baltimore, MD; ⁹Children's Hospital at Montefiore, Division of Pediatric Hematology, Oncology, and Cellular Therapies, Albert Einstein College of Medicine, Bronx, NY; ¹⁰Division of Hematology/Oncology, Department of Medicine, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY; ¹¹Department of Medicine, College of Physicians and Surgeons and ¹²Division of Infectious Diseases, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY; ¹³Research and Development at United Health Group, Minneapolis, MN; ¹⁴PhuHealth, NY, Lake Success, NY; ¹⁵Department of Medicine, McGill University, Montreal, QC, Canada; ¹⁶Thrombosis and Hemostasis, Department of Medicine, Leiden University Medical Center, Leiden, The Netherlands; ¹⁷Section of Hematology, School of Medicine, Yale University, New Haven, CT; ¹⁸Department of Internal Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile; ¹⁹Division of Hematology and Oncology, Kaiser Permanente, Oakland/Richmond, CA; ²⁰Department of Medicine, McMaster University, Hamilton, ON, Canada; ²¹Division of Angiology and Hemostasis, Faculty of Medicine, Geneva University Hospitals, University of Geneva, Geneva, Switzerland; ²²Department of Medicine, Washington University School of Medicine St. Louis, St. Louis, MO; ²³Department of Medicine and ²⁴Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; ²⁵Carriage Grove, MN; ²⁶Toronto, ON, Canada; ²⁷Department of Internal Medicine, American University of Beirut, Beirut, Lebanon; ²⁸Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada; ²⁹Clinical Research Institute, American University of Beirut, Beirut, Lebanon; ³⁰Library Services, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada; ³¹Department of Clinical Medicine, Health Science Center, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico; ³²Office of Scientific Affairs and Research, King Hussein Cancer Center, Amman, Jordan; ³³Department of Neurology, University of Chicago, Chicago, IL; ³⁴The Michael G. DeGroote National Pain Center, McMaster University, Hamilton, ON, Canada; ³⁵Medizinische Fakultät, Albert-Ludwigs-Universität Freiburg, Freiburg, Germany; ³⁶Department of Internal Medicine, Division of Nephrology, University of Kansas Medical Center, Kansas City, KS; and ³⁷Institute for Evidence in 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: These 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 5 November 2020; accepted 18 December 2020; published online XXX. DOI: 10.1182/bloodadvances.2020003763. The full-text version of this article contains a data supplement. © 2021 by The American Society of Hematology



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

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



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 84 lower to 400) fewer 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 81 lower to 480) fewer per 10000 patients	RR 0.92 (0.81 to 1.00)	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

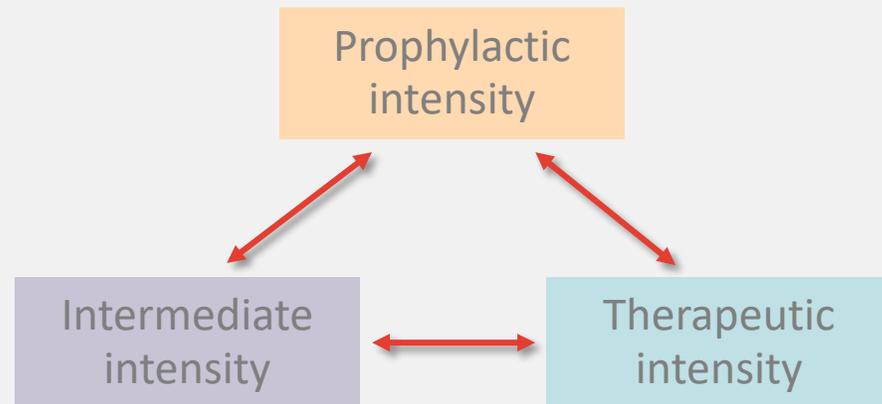
Recommendation/Decision Guideline/coverage decision

Evidence synthesis (systematic review/HTA)

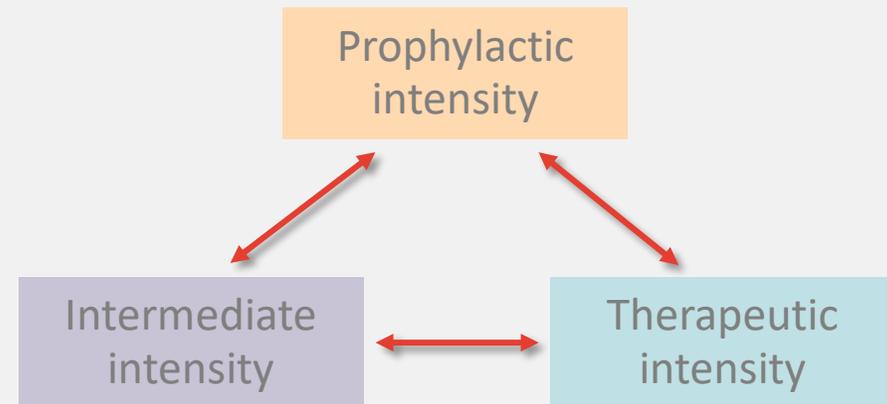
PICO Question Generation & Prioritization

- 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.gradeopro.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

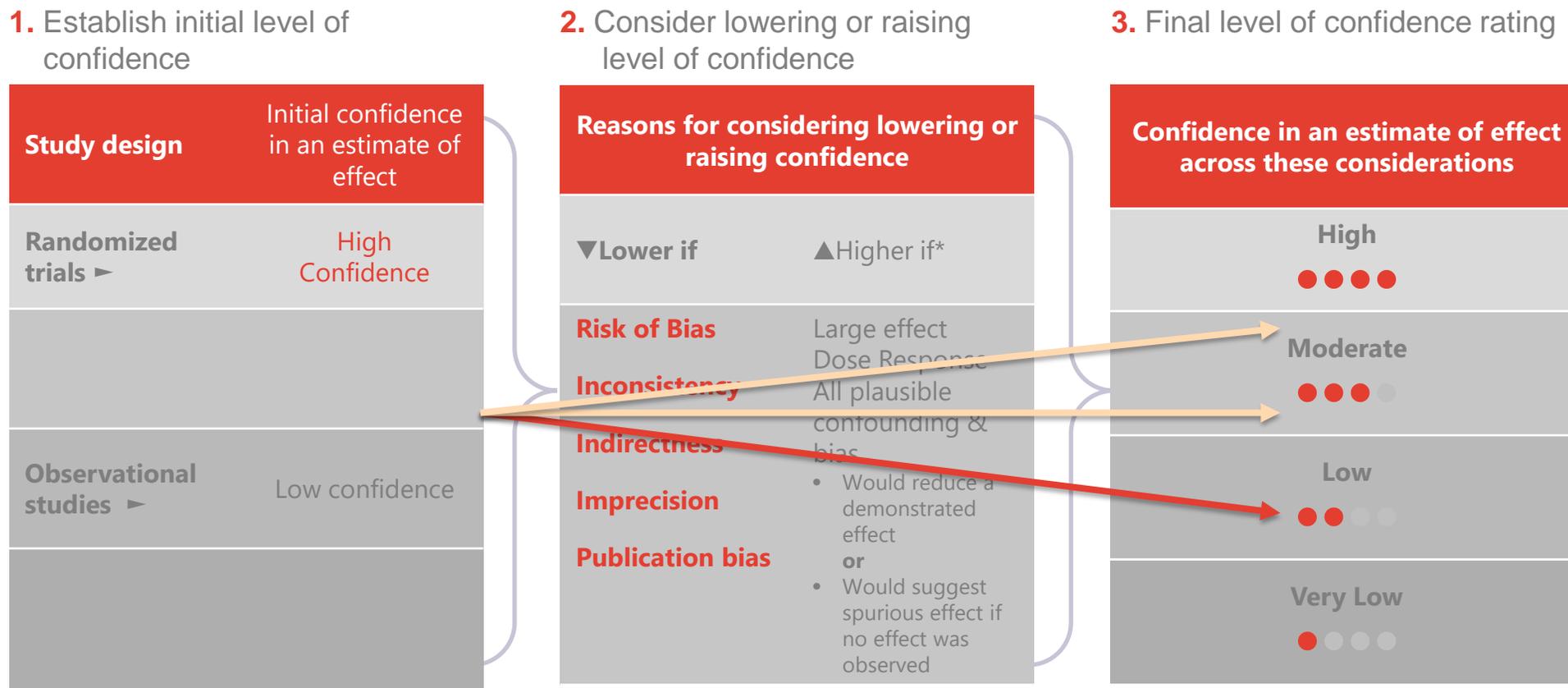
3 per 1,000 fewer



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)



*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)

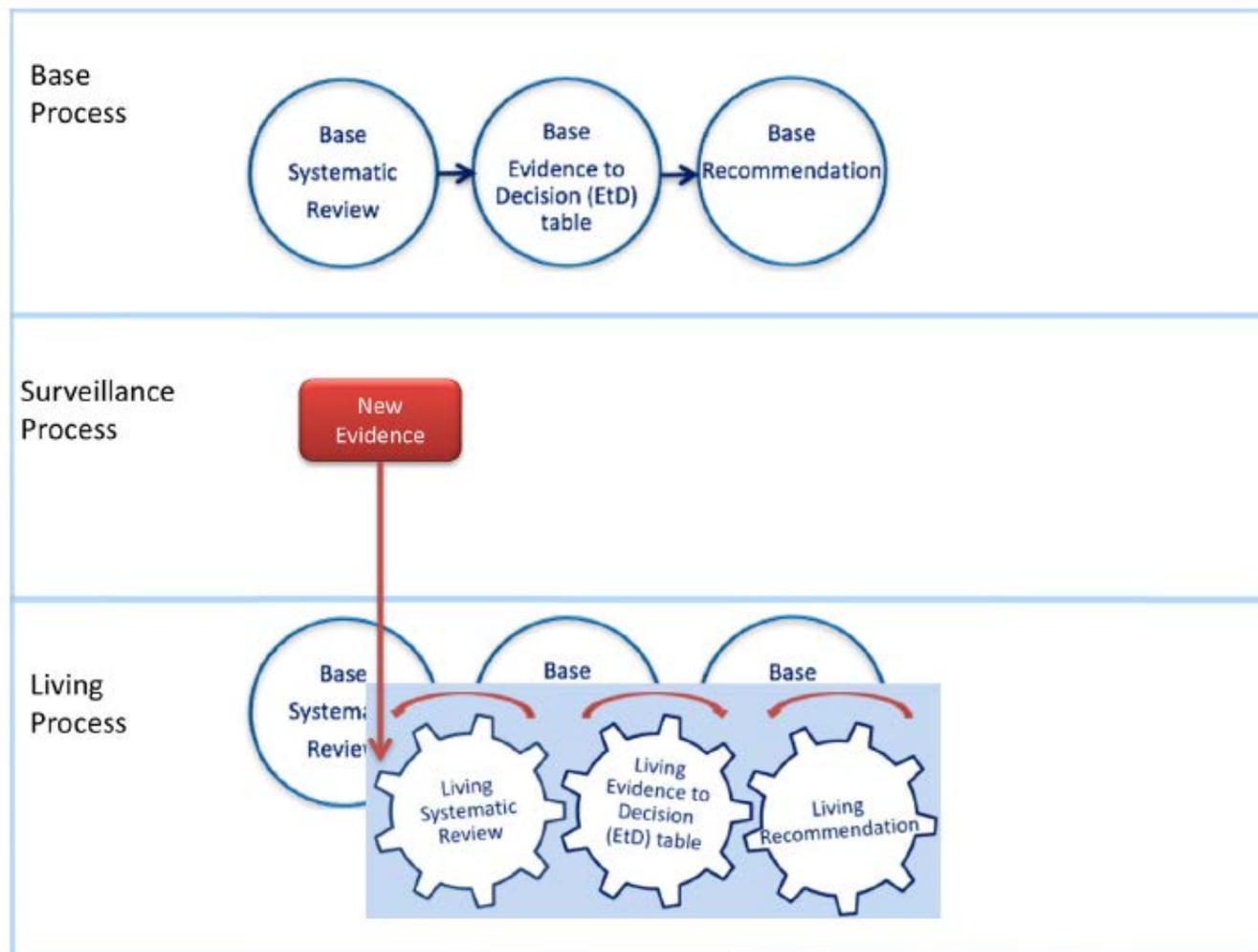


Living Phase – Recommendations

- 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



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

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



Main Challenges

Evidence

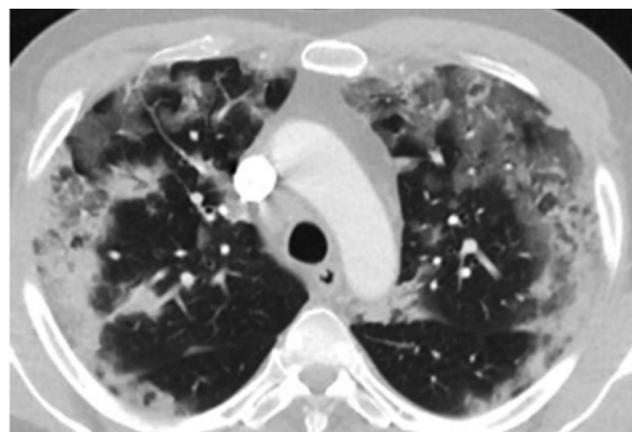
- Large number of citations
- Incomplete reporting
- Risk of bias
- Imprecision
- Evolving field in Living phase

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

Patient T
♂, Chinese, 73 years
BMI 34 kg/m ² , DM, hypertension
COVID-19 day 10
High fever, dyspneic at rest
HR 123/min, RR 42/min, Sat 83% at 15L O ₂



Patient K
♂, Caucasian, 52 years
BMI 23 kg/m ² , 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?

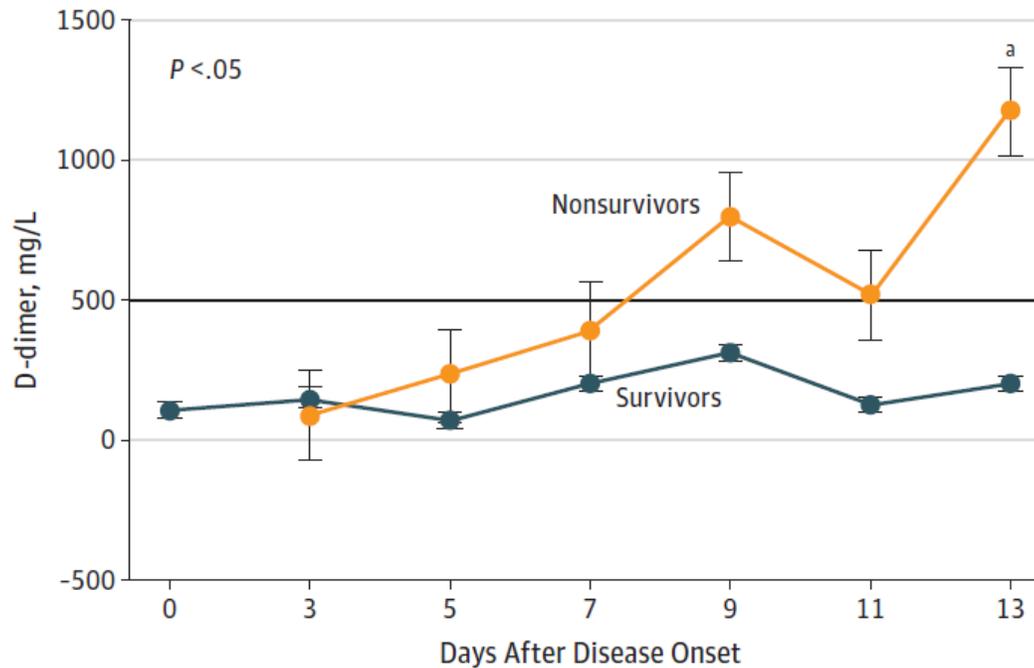


Which ONE of the following options would you suggest for thromboprophylaxis during this medical inpatient's hospital admission?

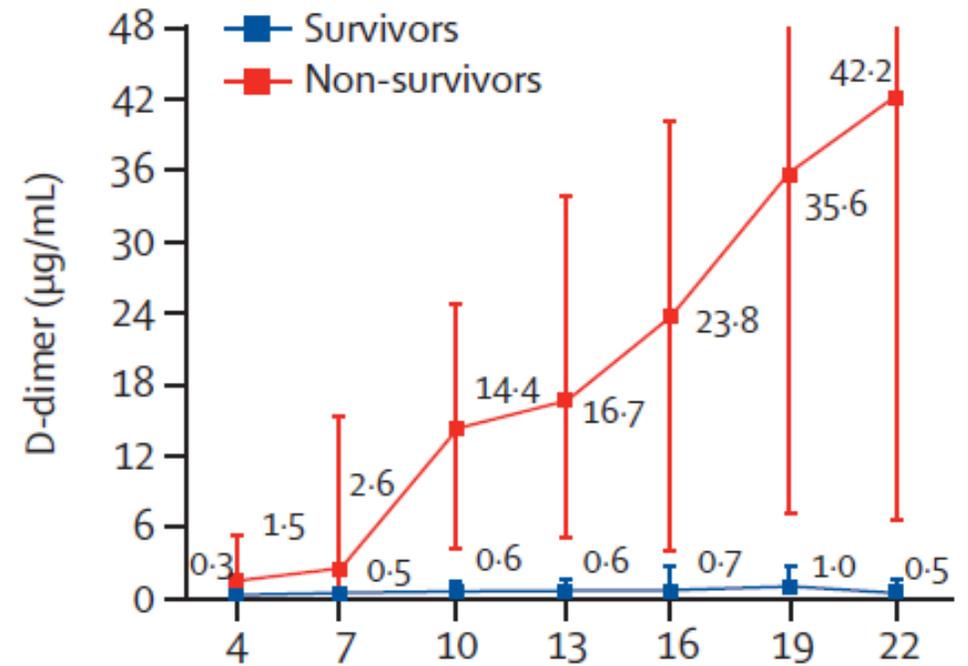
- A. Subcutaneous low molecular weight heparin (LMWH)
- B. Direct oral anticoagulant (Rivaroxaban, or Apixaban)
- C. Graduated compression stockings
- D. No prophylaxis because patient is low thrombosis risk



COVID-19 coagulopathy: initial reports (China)



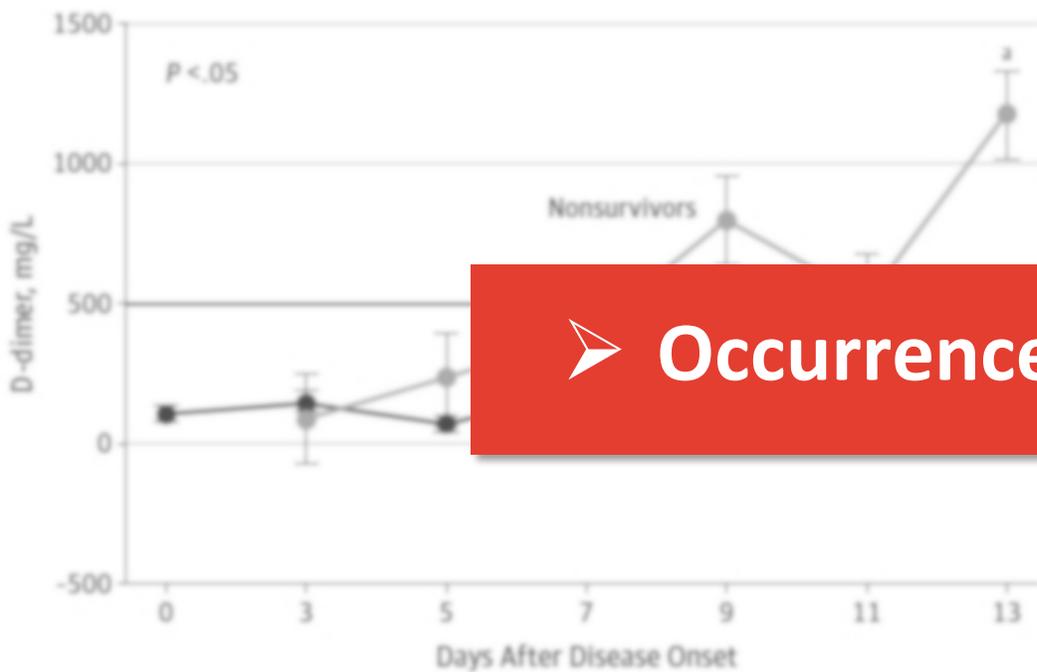
Wang D *et al*, JAMA 2020



Zhou F *et al*, Lancet 2020



COVID-19 coagulopathy: initial reports (China)



➤ Occurrence of VTE not mentioned

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

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

F.A. Klok^{a,*}, M.J.H.A. Kruip^b, N.J.M. van der Meer^{c,d}, M.S. Arbous^e, D. Gommers^f, K.M. Kant^g, F.H.J. Kaptein^a, J. van Paassen^e, M.A.M. Stals^a, M.V. Huisman^{a,1}, H. Endeman^{f,1}

BRIEF REPORT

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

Jean-François Llitjos¹ | Maxime Leclerc² | Camille Chochois² | Jean-Michel Monsallier³ | Michel Ramakers² | Malika Auvray² | Karim Merouani³

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^{1,2}, Charles Tacquard³, François Severac⁴, Ian Leonard-Lorant⁵, Mickaël Ohana⁵, Xavier Delabranche³, Hamid Merdji^{1,6}, Raphaël Clere-Jehl^{1,2}, Malika Schenck⁷, Florence Fagot Gandet⁷, Samira Fafi-Kremer^{2,8}, Vincent Castelain⁷, Francis Schneider⁷, Lélia Grunebaum⁹, Eduardo Anglés-Cano¹⁰, Laurent Sattler⁹, Paul-Michel Mertes³, Ferhat Meziani^{1,6*} 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

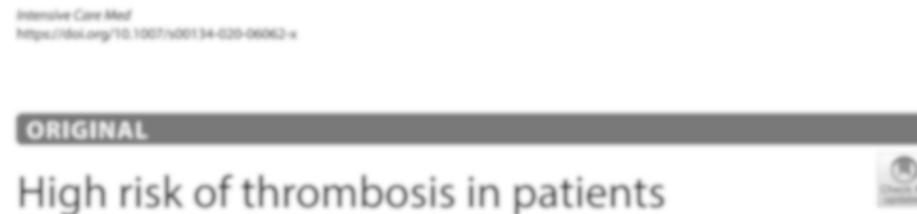
journal homepage: www.elsevier.com/locate/thromres

Full Length Article

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

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

COVID-19 coagulopathy: initial reports (Europe)



➤ Incidence of VTE in ICU 17-70%

Confirmation of the high incidence of venous thromboembolism in critically ill ICU patients
F.A. Klok^{1,2}, M.J.H.A. Kruijff¹, F.H.J. Kaptein¹, J. van Paassen¹

Mickaël Ohana¹, Xavier Delabranche¹, Gander², Samira Fafi-Kremer^{2,3}, Agnès-Cano^{1,3}, Laurent Sattler⁴, Valérie Michel-Merles⁵, Ferhat Meziane^{6,7} and CRICS-THROCESEP 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 Llitjos¹ | Maxime Leclerc² | Camille Chochois² | Jean-Michel Monsallier³ | Michel Ramakers² | Malika Auvray² | Karim Merouani³

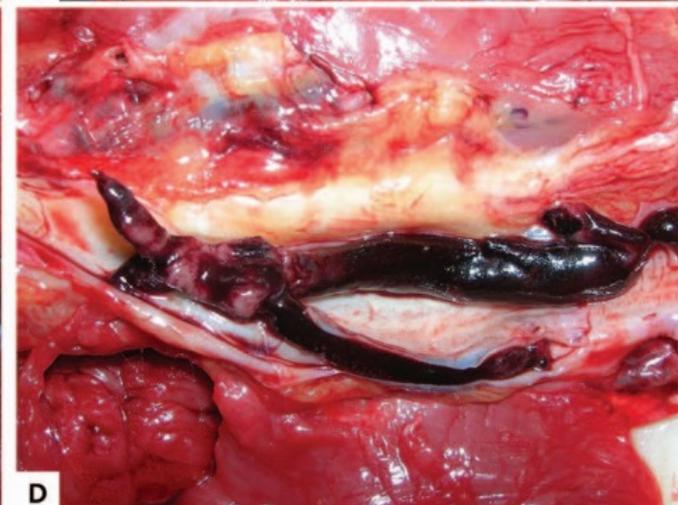
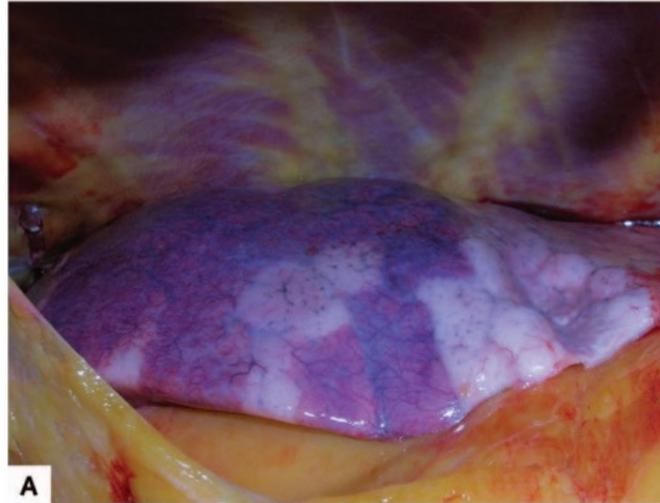


Full Length Article
Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy
Corrado Lodigiani^{1,2,3}, Giacomo Iapichino¹, Luca Carenzo¹, Maurizio Cecconi^{1,2}, Paola Ferrazzi¹, Tim Sebastian⁴, Nils Kucher⁵, Jan-Dirk Studt⁶, Clara Sacco⁷, Bertuzzi Alexia⁸, Maria Teresa Sandri⁹, Stefano Barco¹⁰, 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).

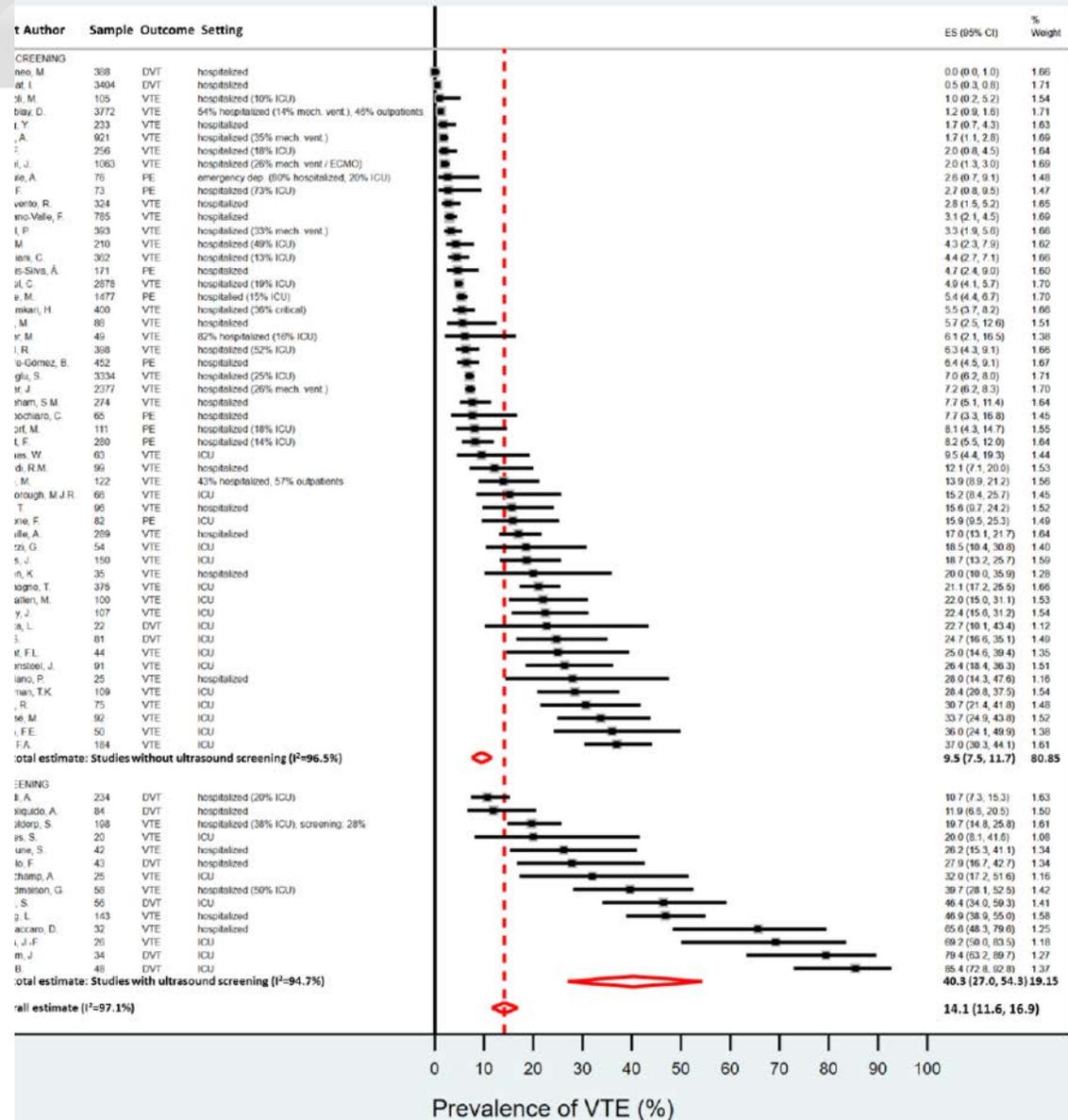




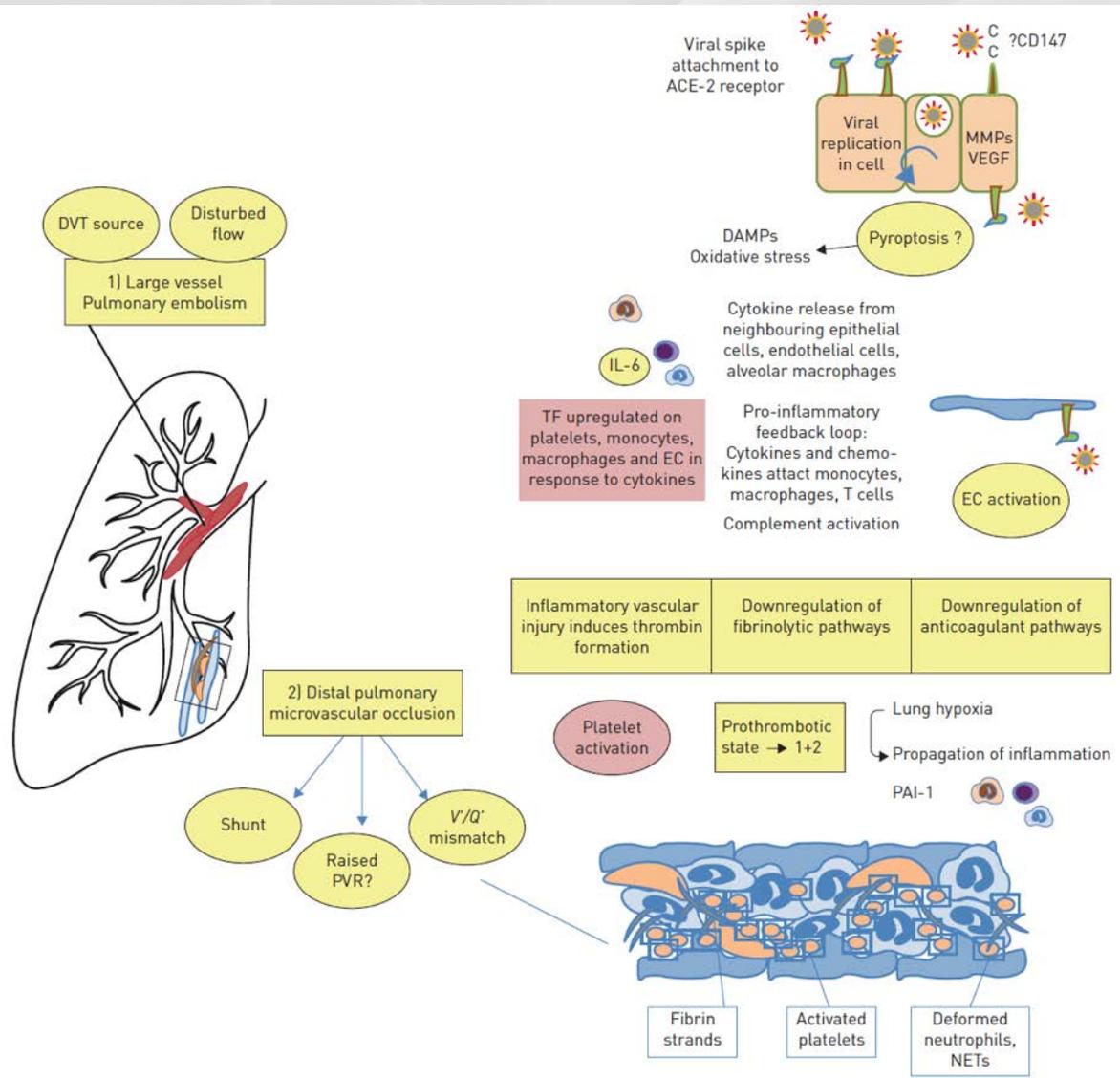
COVID-19: incidence of VTE

➤ 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**

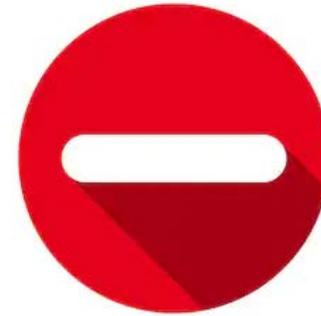


**Inhibits
heparanase**

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

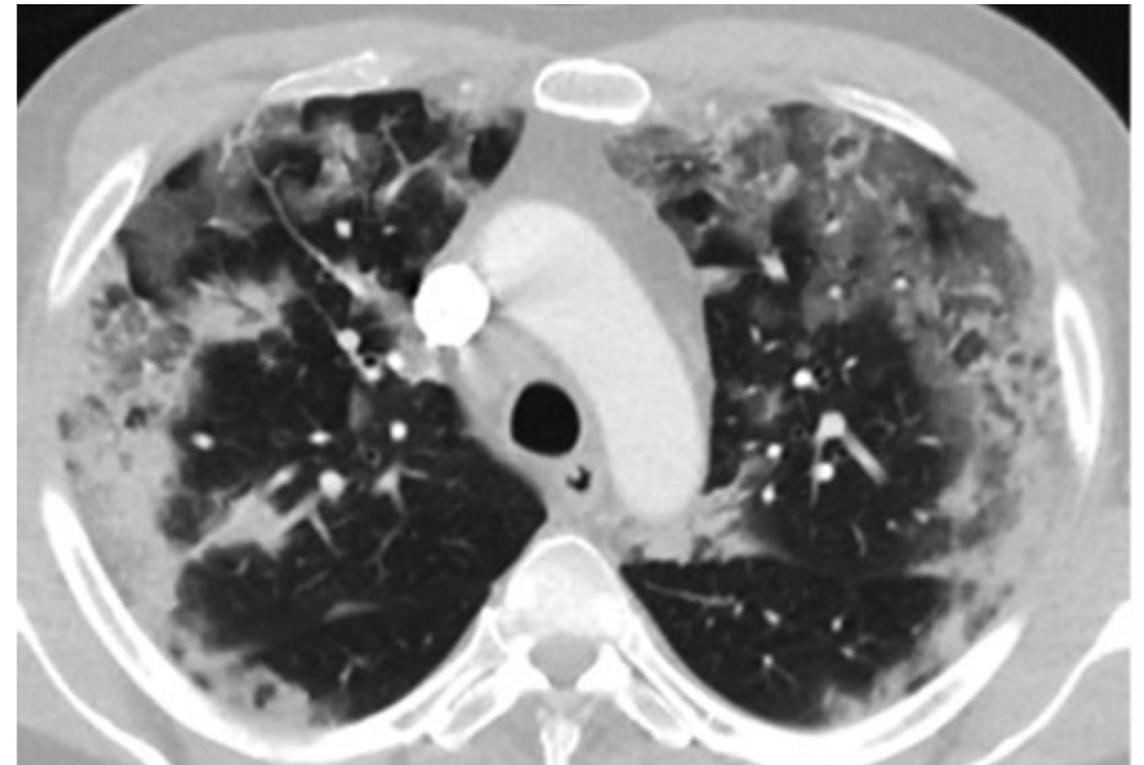
♂, Chinese, 73 years

BMI 34 kg/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?

POPULATION:	Patients with COVID-19 related <i>critical illness</i> 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:	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
MORTALITY 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)
PE 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)
PROXIMAL LOWER EXTREMITY DVT 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)
VTE (DVT or PE) 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)
MAJOR BLEEDING 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)	
				Risk with prophylactic intensity	Risk difference with anticoagulation at intermediate or therapeutic-intensity
MORTALITY 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)
PE 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)
PROXIMAL LOWER EXTREMITY DVT 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)
VTE (DVT or PE) 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)
MAJOR BLEEDING 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	№ 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
MORTALITY 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)
PE 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)
PROXIMAL LOWER EXTREMITY DVT 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)
VTE (DVT or PE) 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)
MAJOR BLEEDING 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)	
				Risk with prophylactic intensity	Risk difference with anticoagulation at intermediate or therapeutic-intensity
MORTALITY 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)
PE 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)
PROXIMAL LOWER EXTREMITY DVT 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)
VTE (DVT or PE) 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)
MAJOR BLEEDING 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)



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

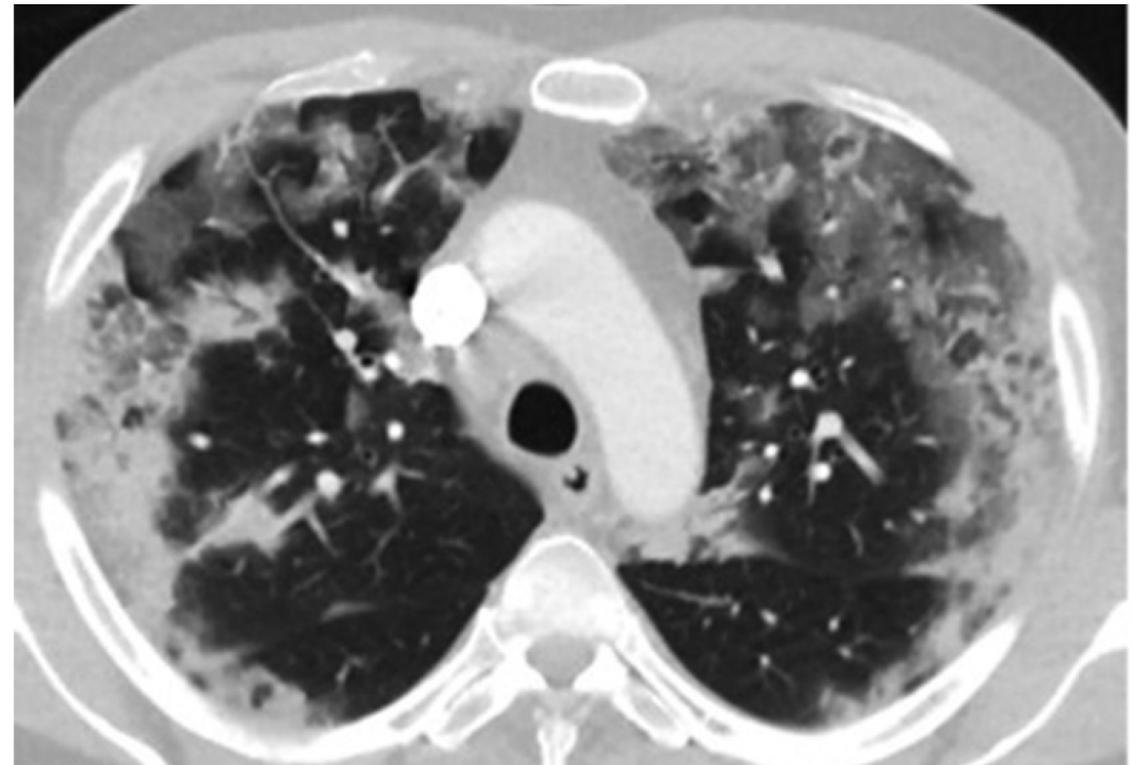
♂, Caucasian, 52 years

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 <i>acute illness</i> 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;

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
ALL-CAUSE MORTALITY 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)
PE 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)
PROXIMAL LOWER EXTREMITY DVT 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)
VTE 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).	
MAJOR BLEEDING 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)	
				Risk with prophylactic-intensity	Risk difference with anticoagulation at intermediate- or therapeutic-intensity
ALL-CAUSE MORTALITY 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)
PE 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)
PROXIMAL LOWER EXTREMITY DVT 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)
VTE follow up: range 6 days to 28 days	0 (1 study)	-	-	Baseline risk (2 studies, range 2.0% to 3.1%).	
MAJOR BLEEDING 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 per 1000 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)	
				Risk with prophylactic-intensity	Risk difference with anticoagulation at intermediate- or therapeutic-intensity
ALL-CAUSE MORTALITY 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)
PE 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)
PROXIMAL LOWER EXTREMITY DVT 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)
VTE follow up: range 6 days to 28 days	0 (1 study)	-	-	Baseline risk (2 studies, range 2.0% to 3.1%).	
MAJOR BLEEDING 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)	
				Risk with prophylactic-intensity	Risk difference with anticoagulation at intermediate- or therapeutic-intensity
ALL-CAUSE MORTALITY 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)
PE 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)
PROXIMAL LOWER EXTREMITY DVT 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)
VTE 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).	
MAJOR BLEEDING 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)	



Recommendation

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