



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

Adam Cuker, Eric K. Tseng, Robby Nieuwlaet, 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





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

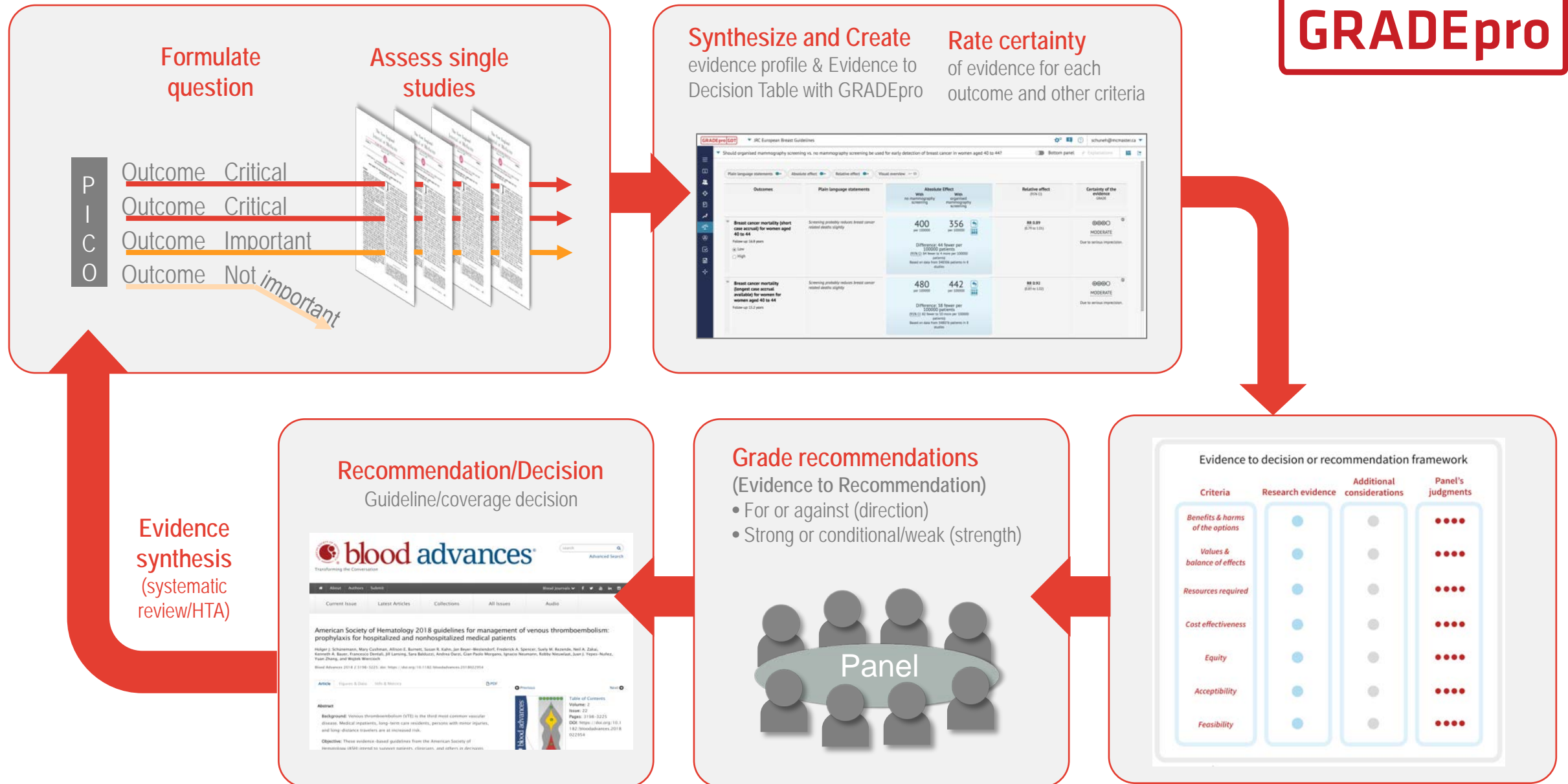
Initial Phase

- 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

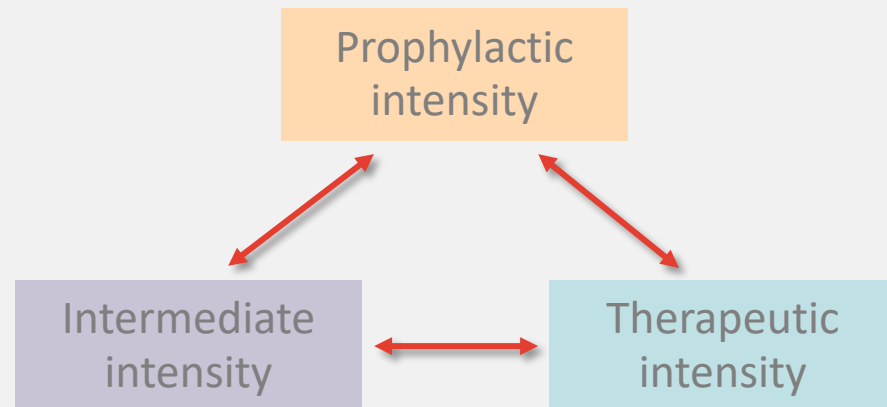




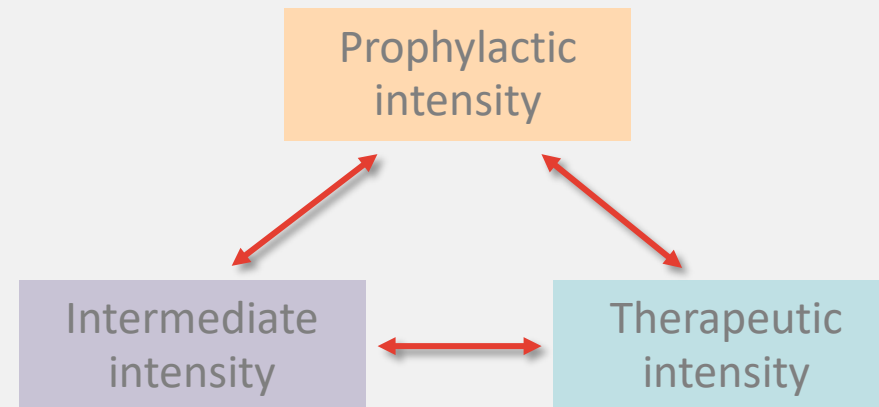
PICO Question Generation & Prioritization

- 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.gradeapro.org/>

Critical Outcomes

- | | |
|--------------------------|--------------------------------------|
| • All-cause mortality | • Intracranial |
| • Pulmonary embolism | hemorrhage/hemorrhagic stroke |
| • Deep venous thrombosis | • Invasive mechanical ventilation |
| • Major bleeding | • Limb amputation |
| • Multi-organ failure | • ICU admission |
| • Ischemic stroke | • 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*
Risk of Bias	Large effect
Inconsistency	Dose Response
Indirectness	All plausible confounding & bias
Imprecision	• Would reduce a demonstrated effect
Publication bias	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

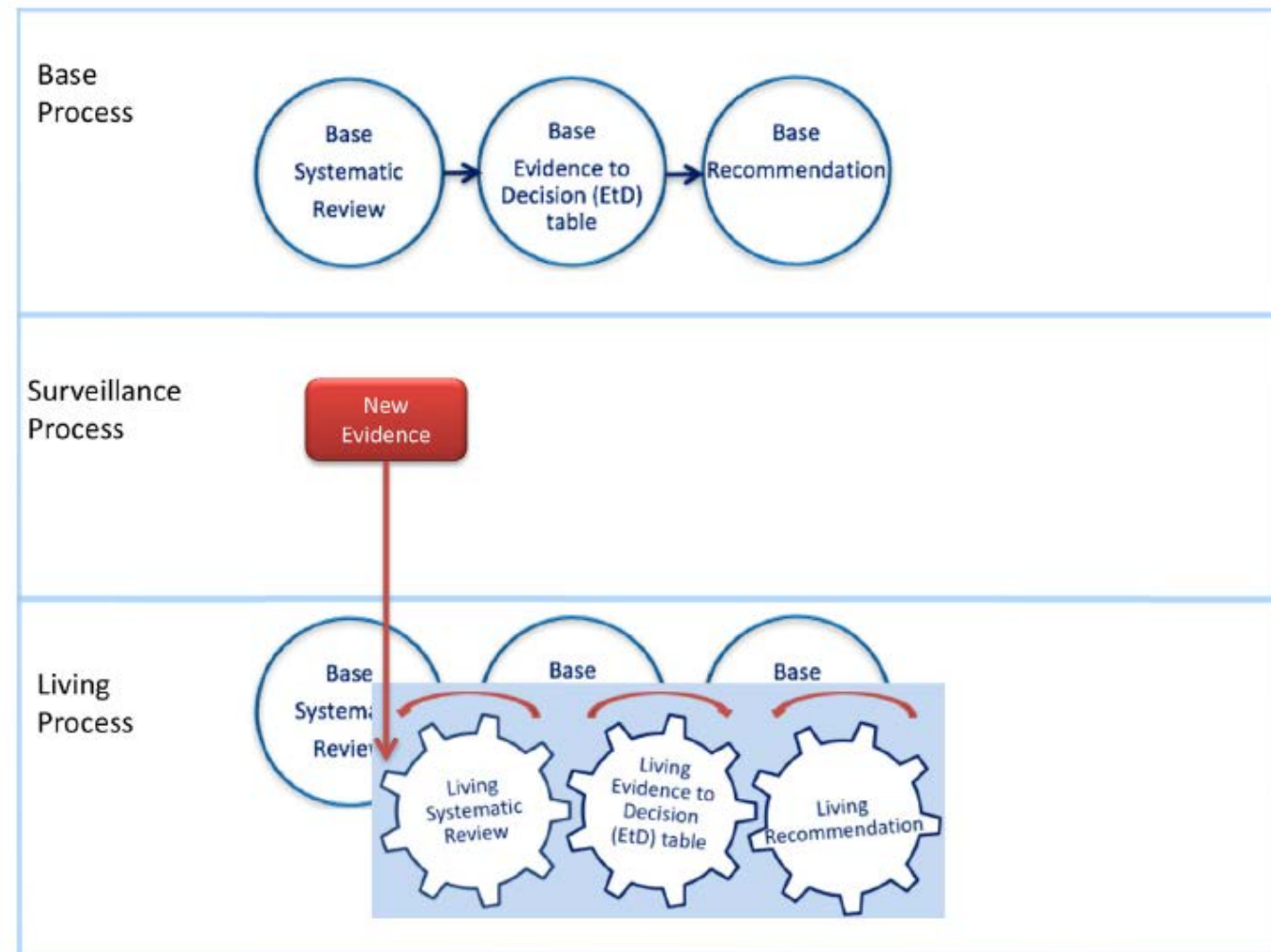


Fig. 2. The main steps of the living guideline process, focused on the unit of update, that is, the living recommendation.

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

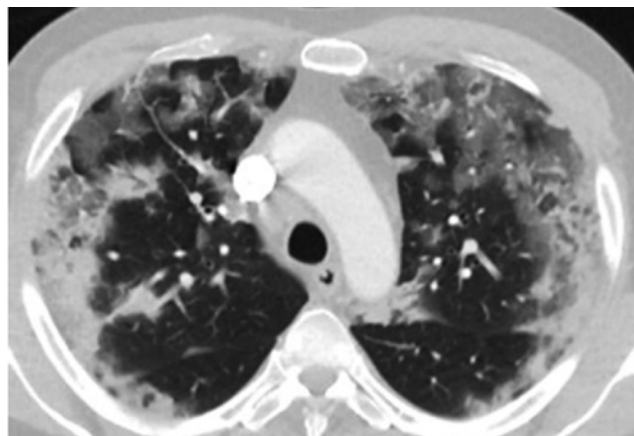
♂, Chinese, 73 years

BMI 34 kg/m², DM, hypertension

COVID-19 day 10

High fever, dyspneic at rest

HR 123/min, RR 42/min, Sat 83% at 15L O₂



Patient K

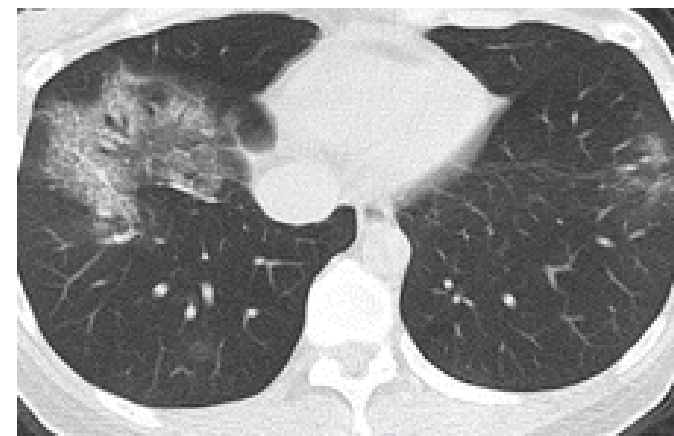
♂, Caucasian, 52 years

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





Million Dollar Question

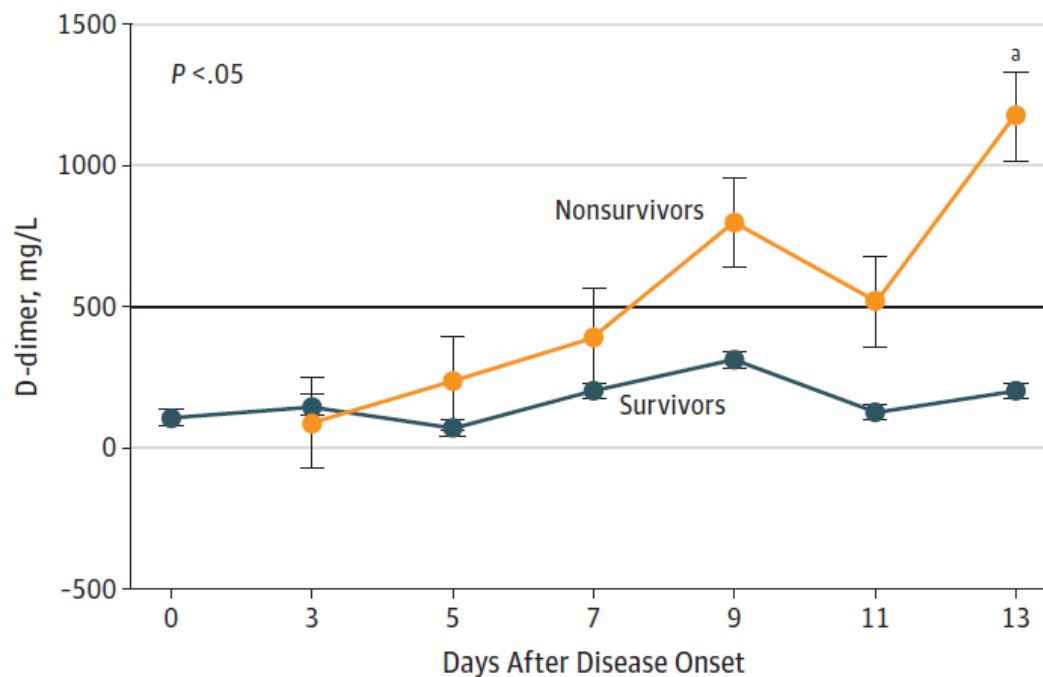
What would be the optimal
anticoagulant strategy in
these 2 patients?



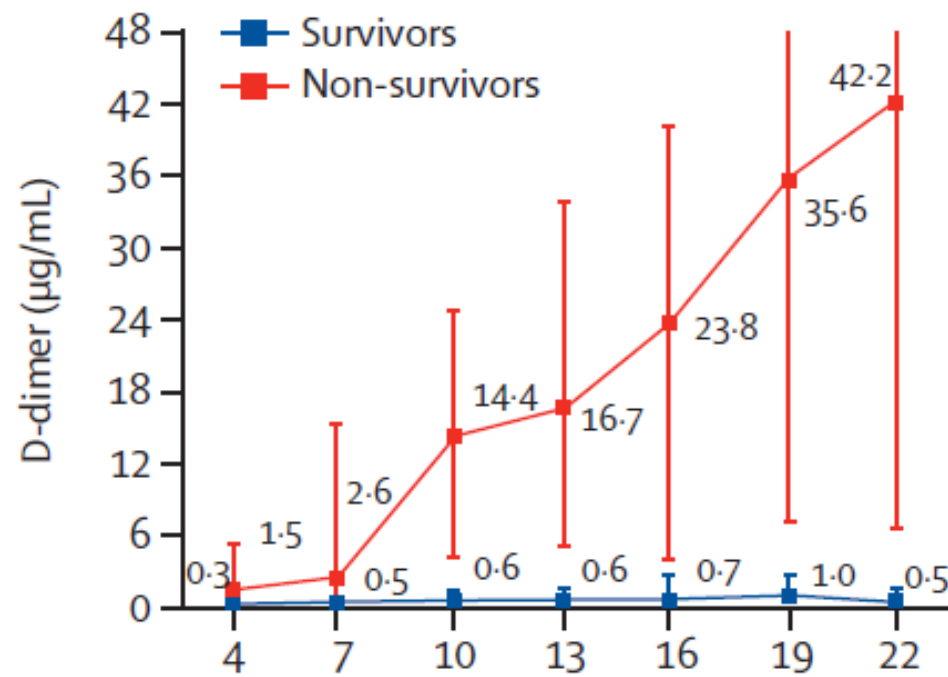
Which ONE of the following options would you suggest for thromboprophylaxis during this medical inpatient's hospital admission?

- 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)

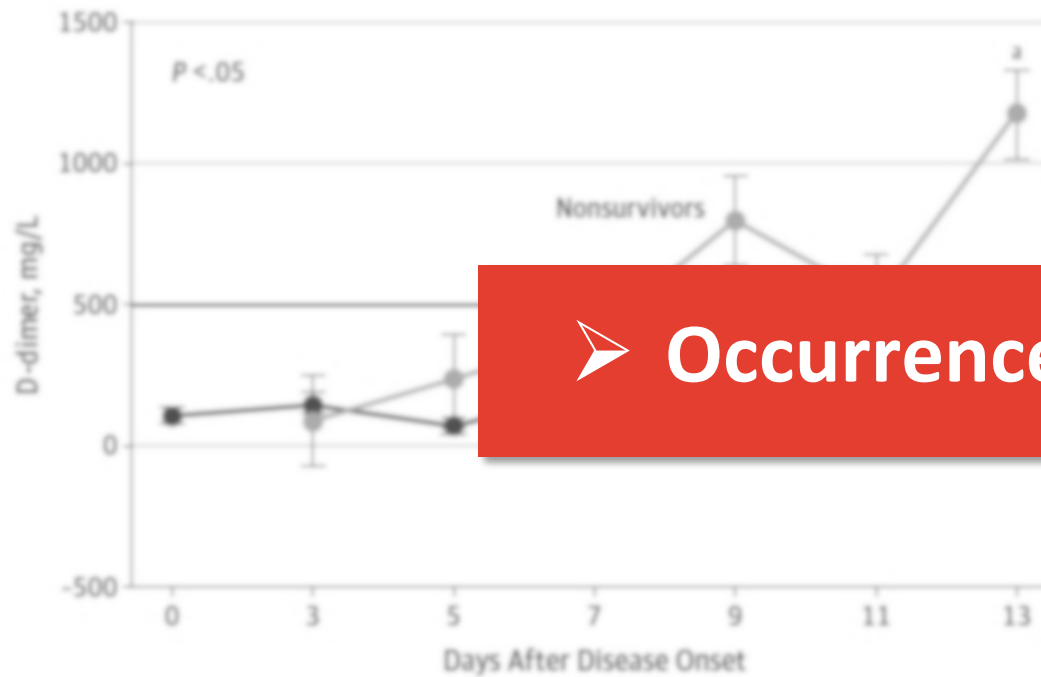


Wang D *et al*, JAMA 2020



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. Kruij^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

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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)



Confirmation of the high
in critically ill ICU patients
F.A. Klok^{1,2}, M.J.H.A. Kruijs¹,
F.H.J. Kaptein¹, J. van Paassen¹

➤ Incidence of VTE in ICU 17-70%

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ORIGINAL

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Mickaël Ohana¹, Xavier Delabranche¹,
Gandet², Samira Fafi-Kremer^{2,3},
Cano^{1,3}, Laurent Sattler³,
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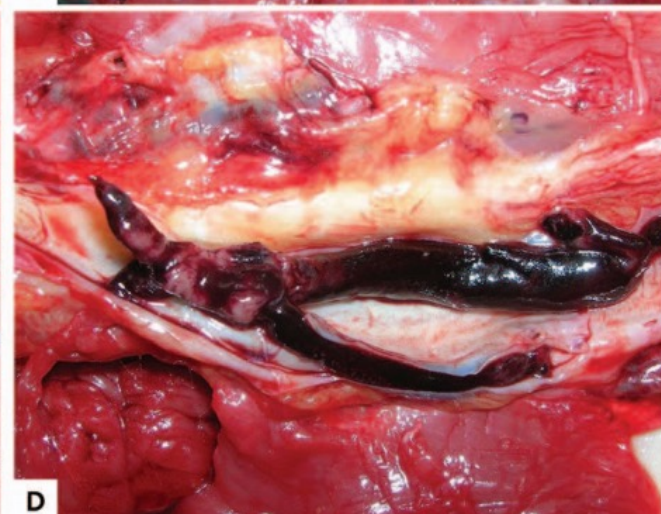
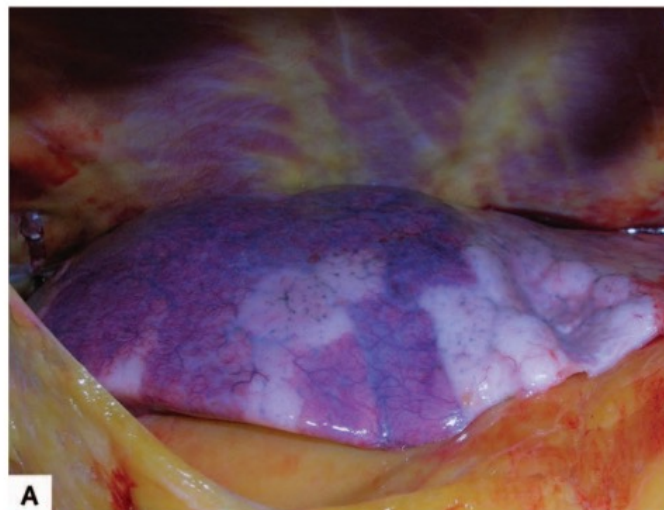
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COVID-19 coagulopathy: autopsy studies

Macroscopic autopsy findings

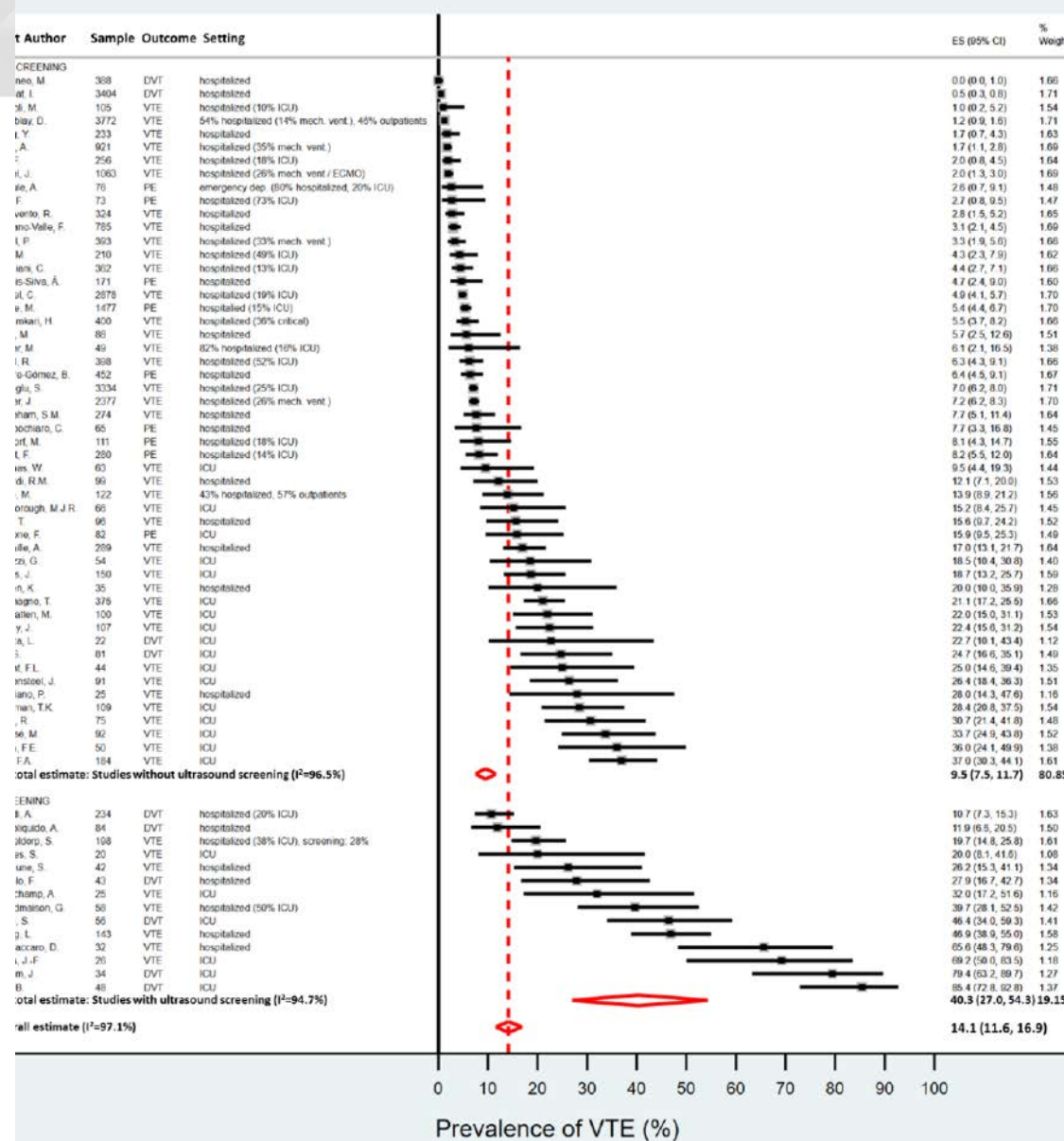
- A. Patchy aspect of the lung surface (case1).
- B. Cutting surface in (case 4).
- C. Pulmonary embolism (case 3).
- D. Deep venous thrombosis (case 5).



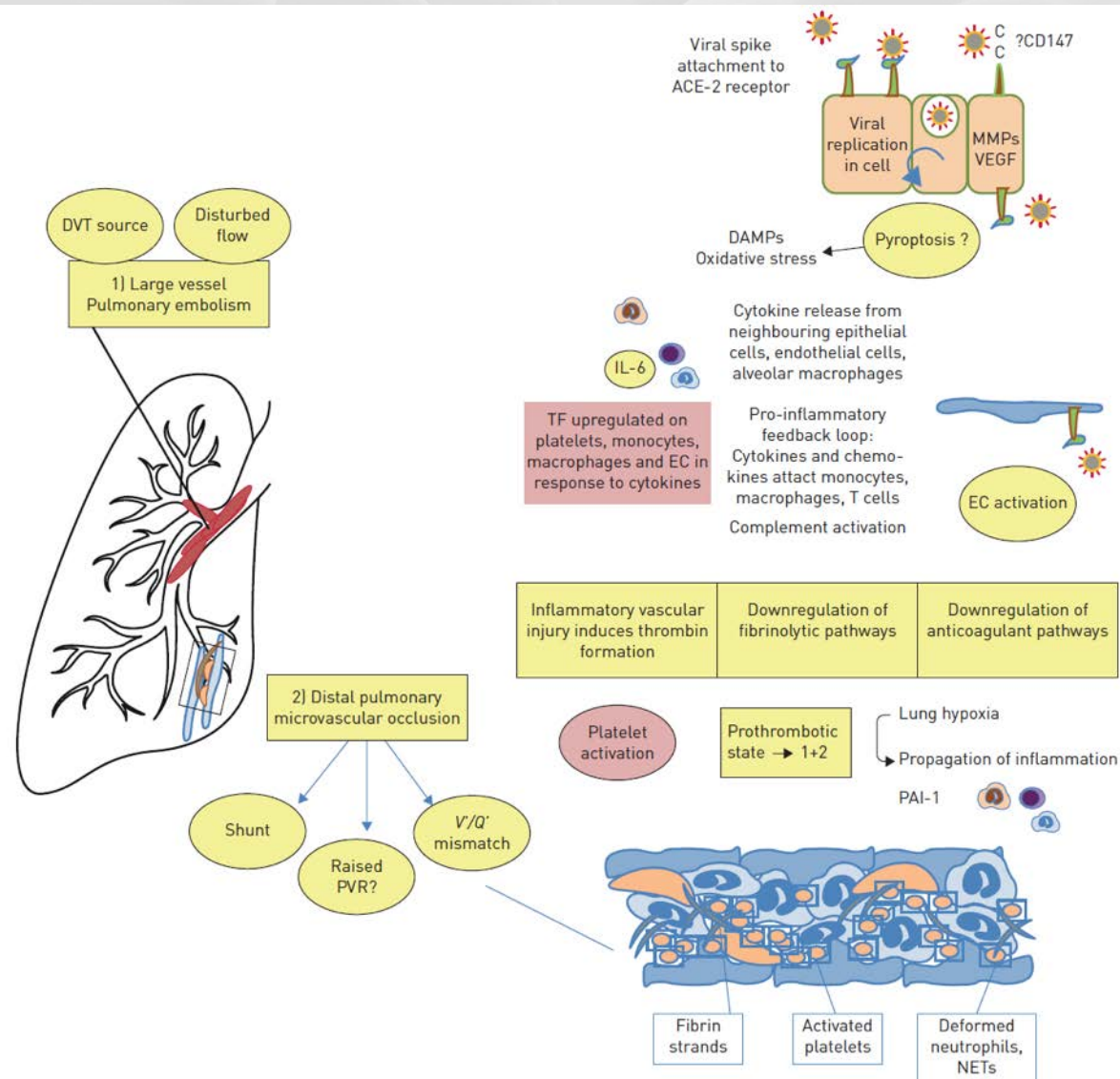
COVID-19: incidence of VTE

➤ 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

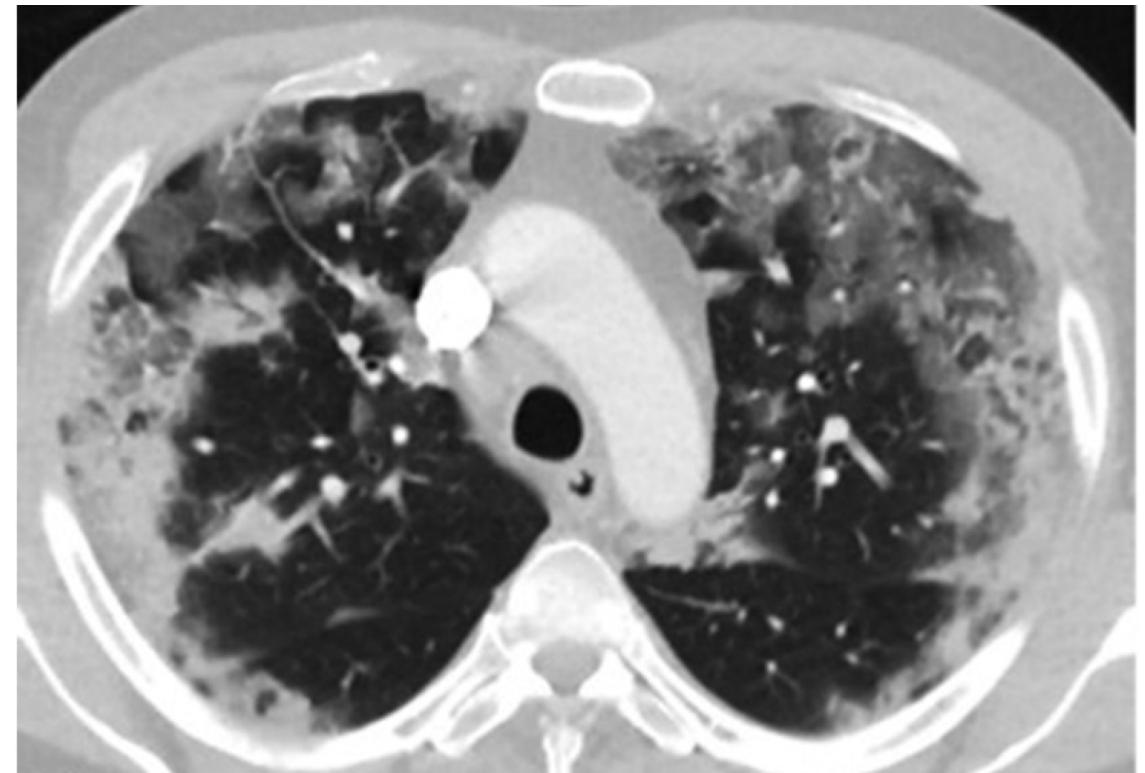
♂, Chinese, 73 years

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)

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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

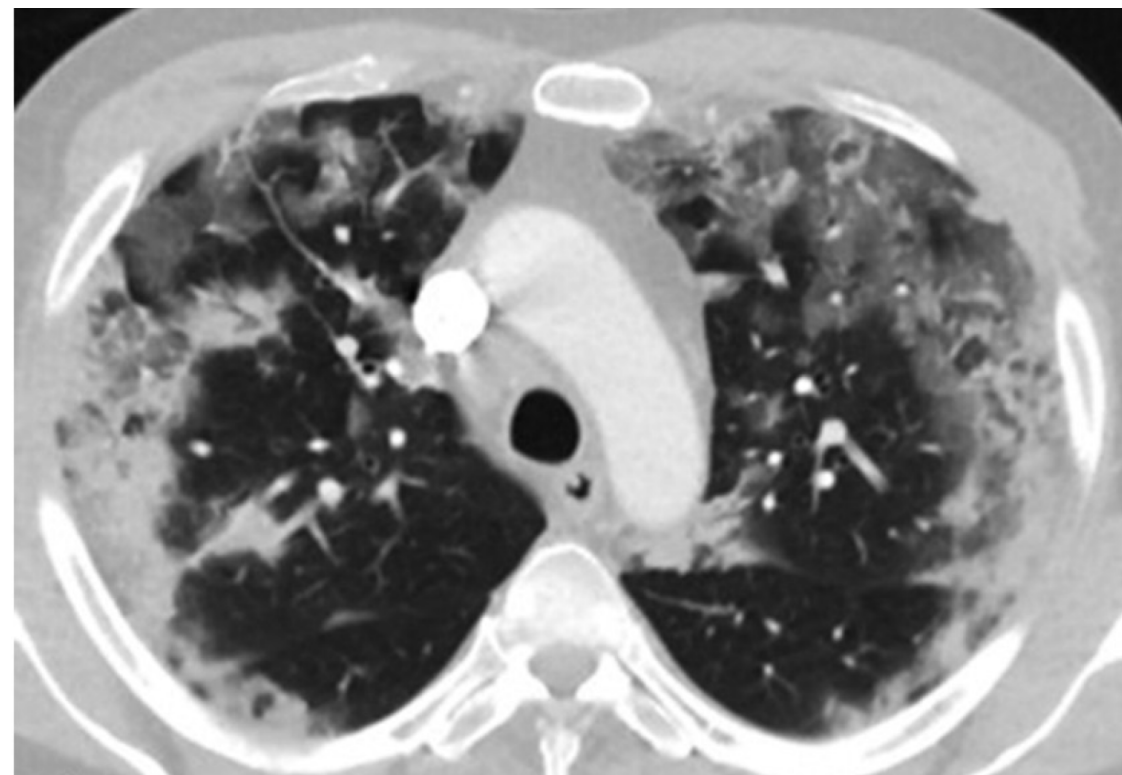
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BMI 23 kg/m², Asthma

COVID-19 day 6

Anosmia, shortness of breath with exercise

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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
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- 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?

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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
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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 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



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