Use of Anticoagulation in Patients with COVID-19

An Educational Slide Set

American Society of Hematology Guidelines on Use of Anticoagulation in Patients with COVID-19

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Clinical Guidelines

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

Deborah M. Siegal, Eric K. Tseng, Holger J. Schünemann, Pantep Angchaisuksiri, Clifton Blair, Adam Cuker, Kathryn Dane, Maria T. DeSancho, David Diuguid, Daniel O. Griffin, Frederikus A. Klok, Alfred Ian Lee, Ignacio Neumann, Ashok Pai, Marc Righini, Kristen M. Sanfilippo, Mike Skara, Deirdra R. Terrell, Kamshad Touri, Elie A. Akl, Reyad Al Jabiri, Yazan Al Jabiri, Romina Brignardello-Petersen, Luis E. Colunga-Lozano, Karin Dearness, Andrea J. Darzi, Samer G. Karam, Gian Paolo Morgano, Rami Z. Morsi, Binu A. Philip, Yetiani Roldan Benitez, Adrienne Stevens, Karla Solo, Wojtek Wiercioch, Reem A. Mustafa, and Robby Nieuwlaat

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

5 **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.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

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 patients

Patients hospitalized for medical illness

Critically ill patients

Patients with immediately life-threatening illness requiring admission to intensive care unit

Discharged patients

Patients who have been discharged after hospitalization for COVID-19

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 and patients who were discharged after hospitalization for 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

3. Describe VTE prophylaxis recommendations for Patients who have been **discharged after hospitalization** for COVID-19 who do not have suspected or confirmed VTE
   - Post-discharge prophylactic intensity anticoagulation

Methods

Overall

- GRADE methodology for 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, prognostic factors, effect of anticoagulation strategies
- Revisiting guideline recommendations if new evidence meets pre-specified criteria

Sunset

GRADEpro

Formulate question

Assess single studies

P
I
C
O

Outcome Critical

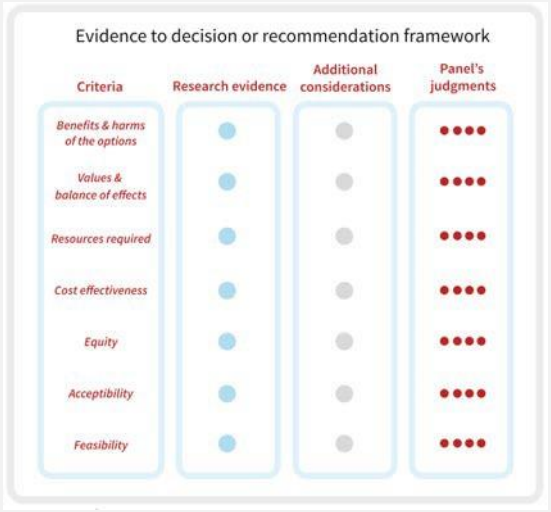
Outcome Critical

Outcome Important

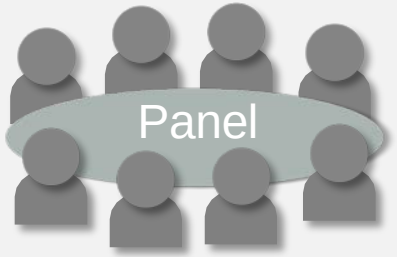
Outcome Not important

Synthesize and Create
evidence profile & Evidence to Decision Table with GRADEpro

Rate certainty
of evidence for each outcome and other criteria



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



Recommendation/Decision
Guideline/coverage decision

Evidence synthesis
(systematic review/HTA)

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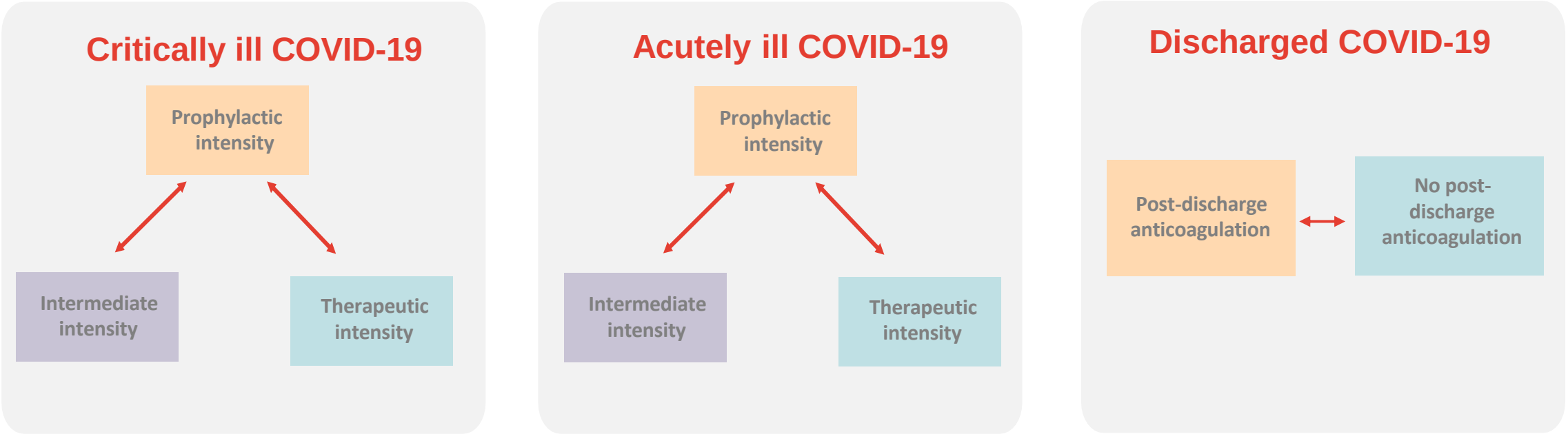
PICO Question Generation & Prioritization

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



Outcome Selection

Brainstorming
- List of potential outcomes

+

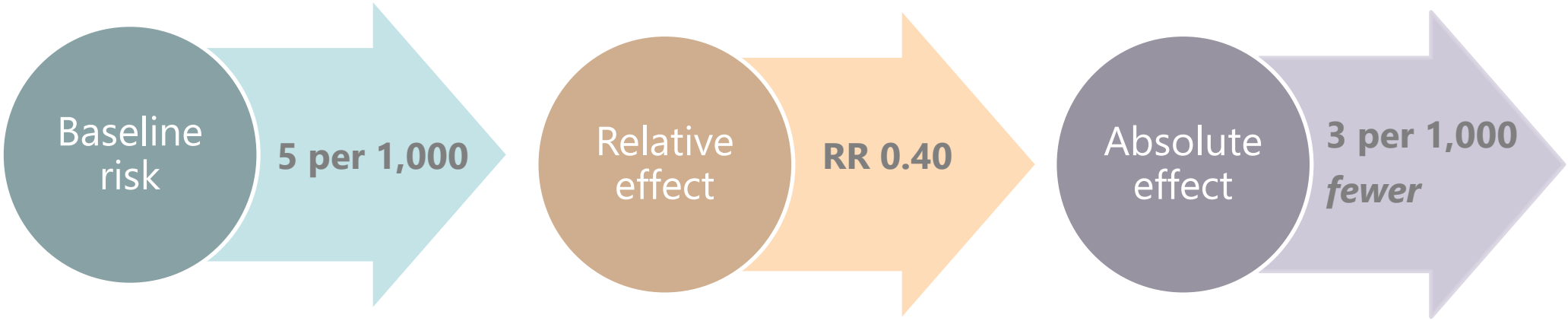
Importance rating
- Most critical for key stakeholders

→

Critical outcomes

All-cause mortality
Pulmonary embolism
Deep venous thrombosis
Major bleeding
- Multi-organ failure
- Ischemic stroke
- Intracranial hemorrhage
- Invasive mechanical ventilation
- Limb amputation
- ICU admission
- STEMI

Evidence for Effect of the Intervention



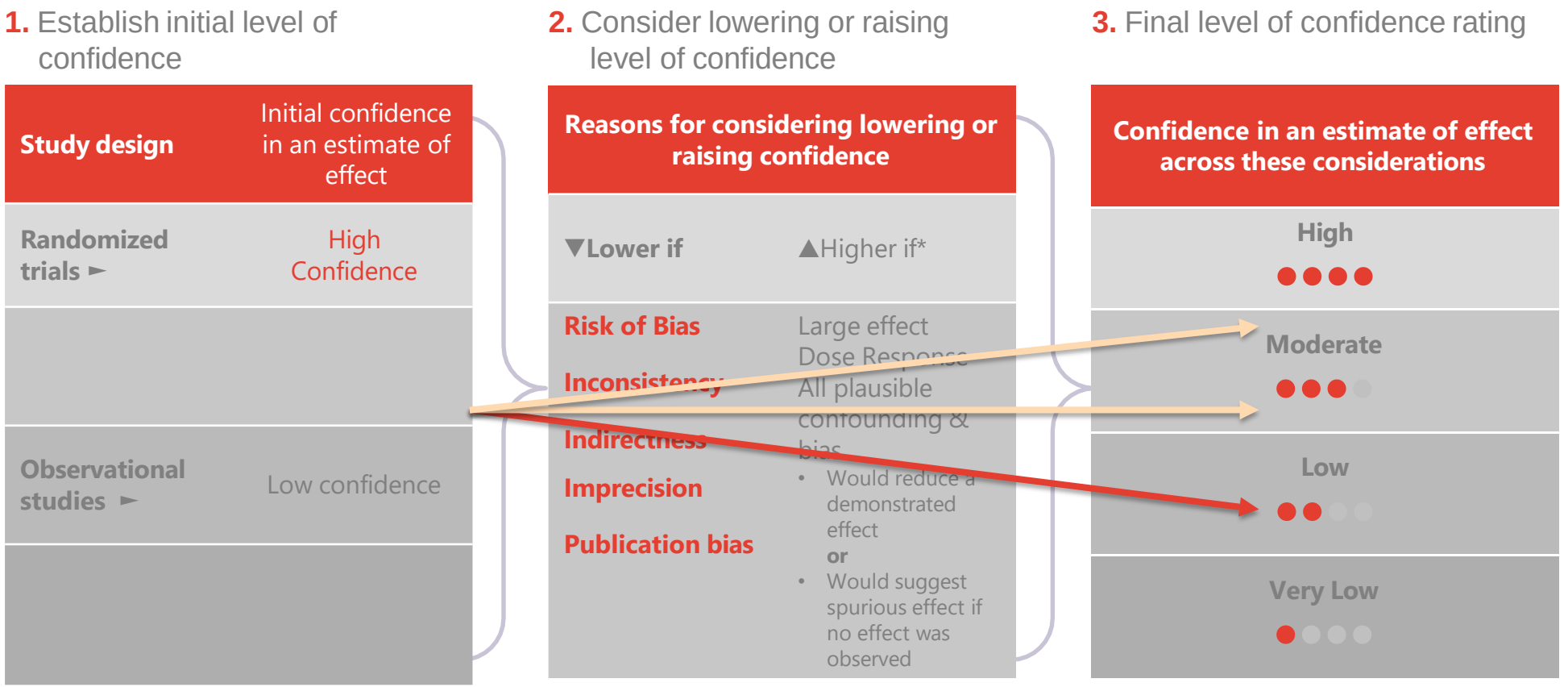
Evidence-to-decision framing

Certainty of Evidence	**Our confidence that the effect estimate is adequate** to support a recommendation (high, moderate, low, very low) Reflects strengths and limitations of the evidence (study design, risk of bias, imprecision, inconsistency, indirectness, publication bias)
Strength of Recommendation	**Extent to which we can be confident** that the desirable effects of an intervention outweigh its undesirable effects Categorized as strong or conditional

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 three populations of interest (critically ill; acutely ill; discharged from hospitalization for COVID-19)
  - Baseline risk assessed among patients receiving prophylactic intensity anticoagulation (for critically ill and acutely ill) and no anticoagulation (for patients discharged from hospital)
- Required:
  - Not high risk of bias (according to simplified QUIPS)
  - Reporting duration of follow-up
- Initial search date: 23-JUL-2020
- Screened through: 31-MAY-2023
- Screened: 28,104 citations
- Included: 148 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 three populations of interest
  - Addressing Prophylactic vs. Intermediate/Therapeutic intensity (for critically and acutely ill) and prophylactic-intensity vs no anticoagulation (for patients discharged from hospital)
- Required:
  - Pre-defined definitions for Prophylactic, Intermediate, Therapeutic intensity
  - Risk of bias assessed with ROBINS-I
- Initial search date: 20-AUG-2020
- Screened through: 31-MAY-2023
- Screened: 17,590 citations
- Included: 22 trials
- 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

- Continued to work closely with panel and systematic review team
- Reconsidered recommendations when important new evidence was identified
- Used 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)
  - Face validity (inclusion of new important trials)
- Published updated recommendations and supporting documents

Timely advice for decision-makers

Living Recommendations

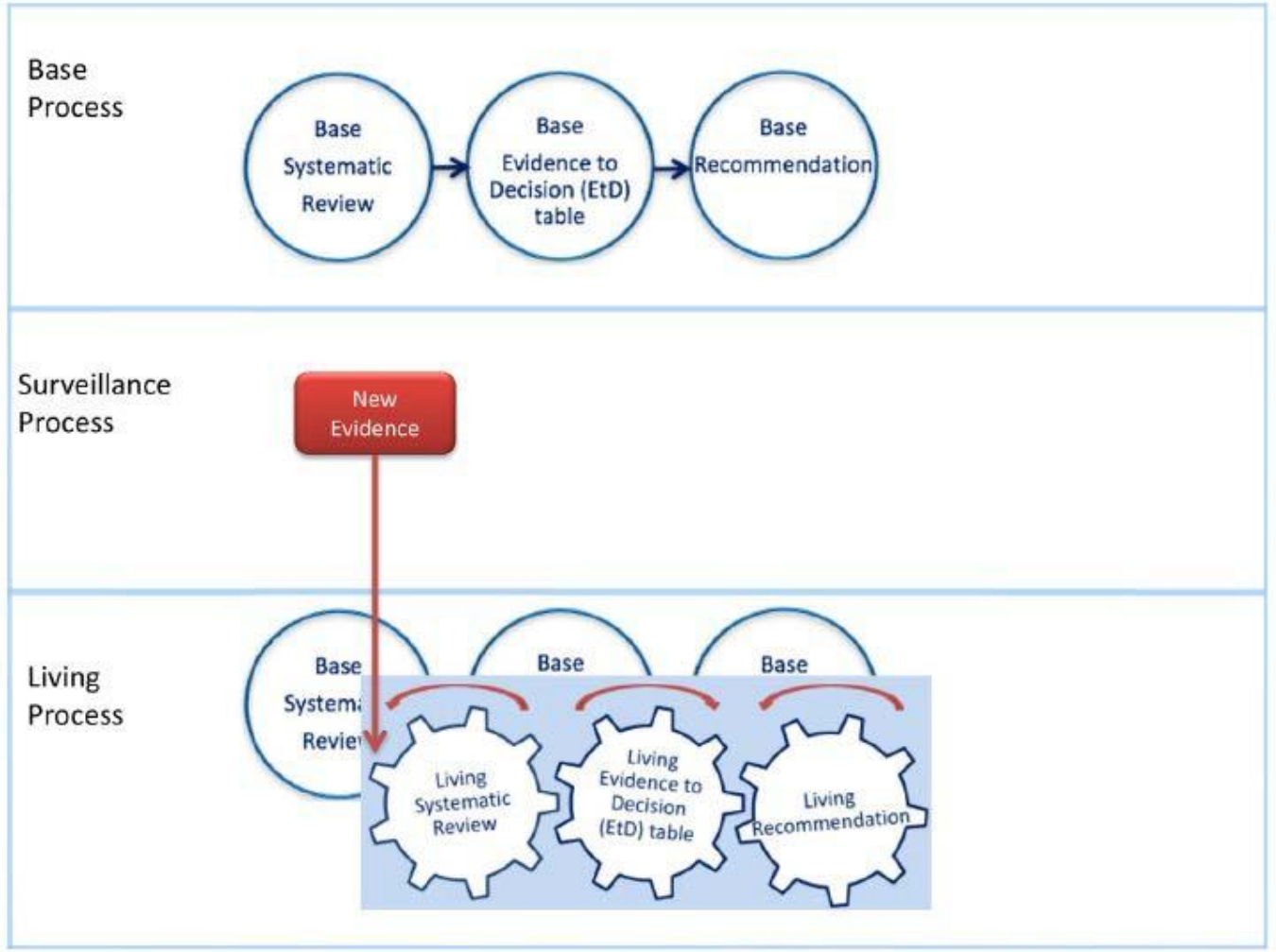


Fig. 2. The main steps of the living guideline process, focused on the unit of update, that is, the living recommendation.

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

Main Methodological 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

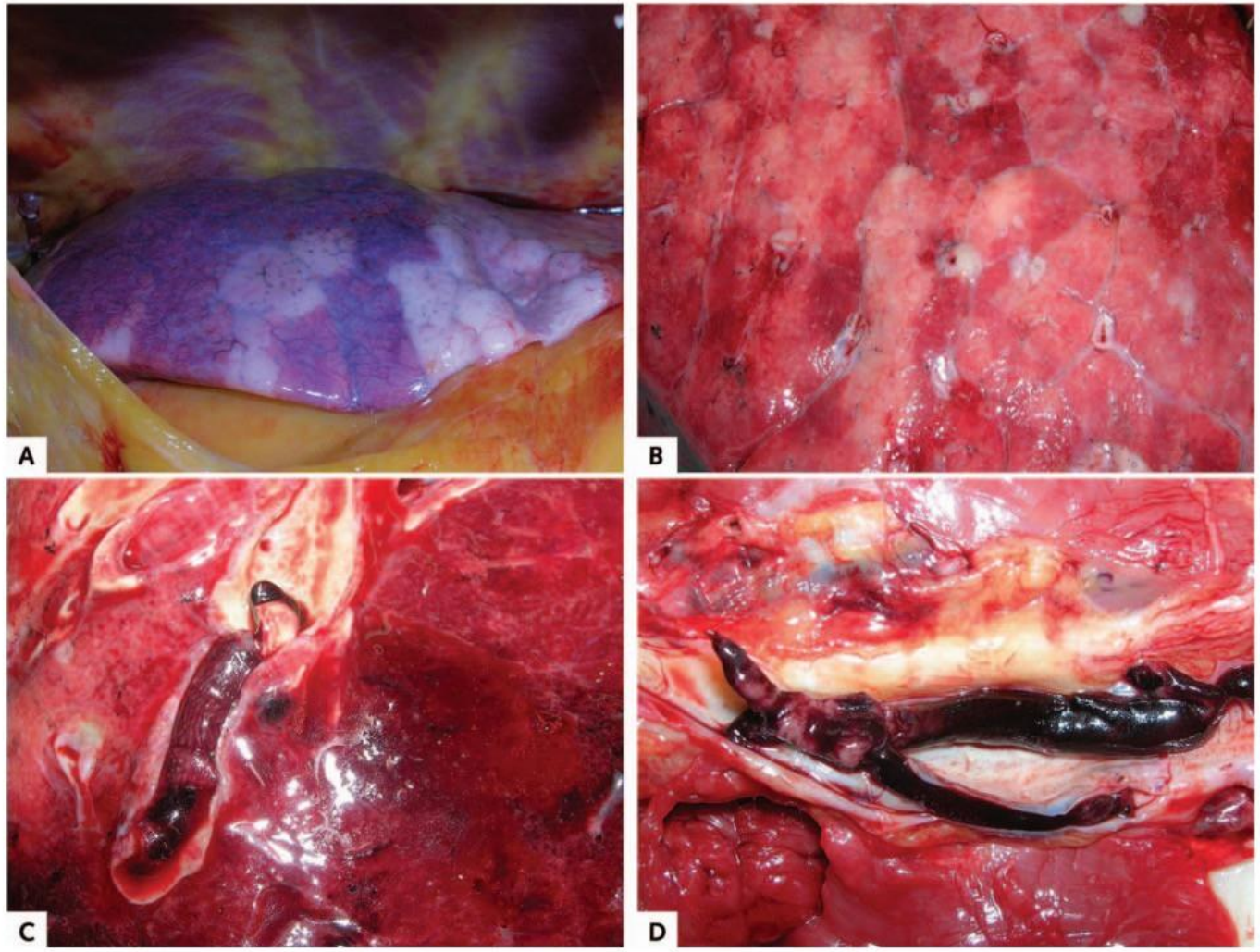
COVID-19 Thrombosis Challenges

1. Defining COVID-19 hypercoagulability
2. Anticoagulation for patients hospitalized for COVID-19
3. Anticoagulation after hospitalization for COVID-19

COVID-19 coagulopathy: autopsy studies

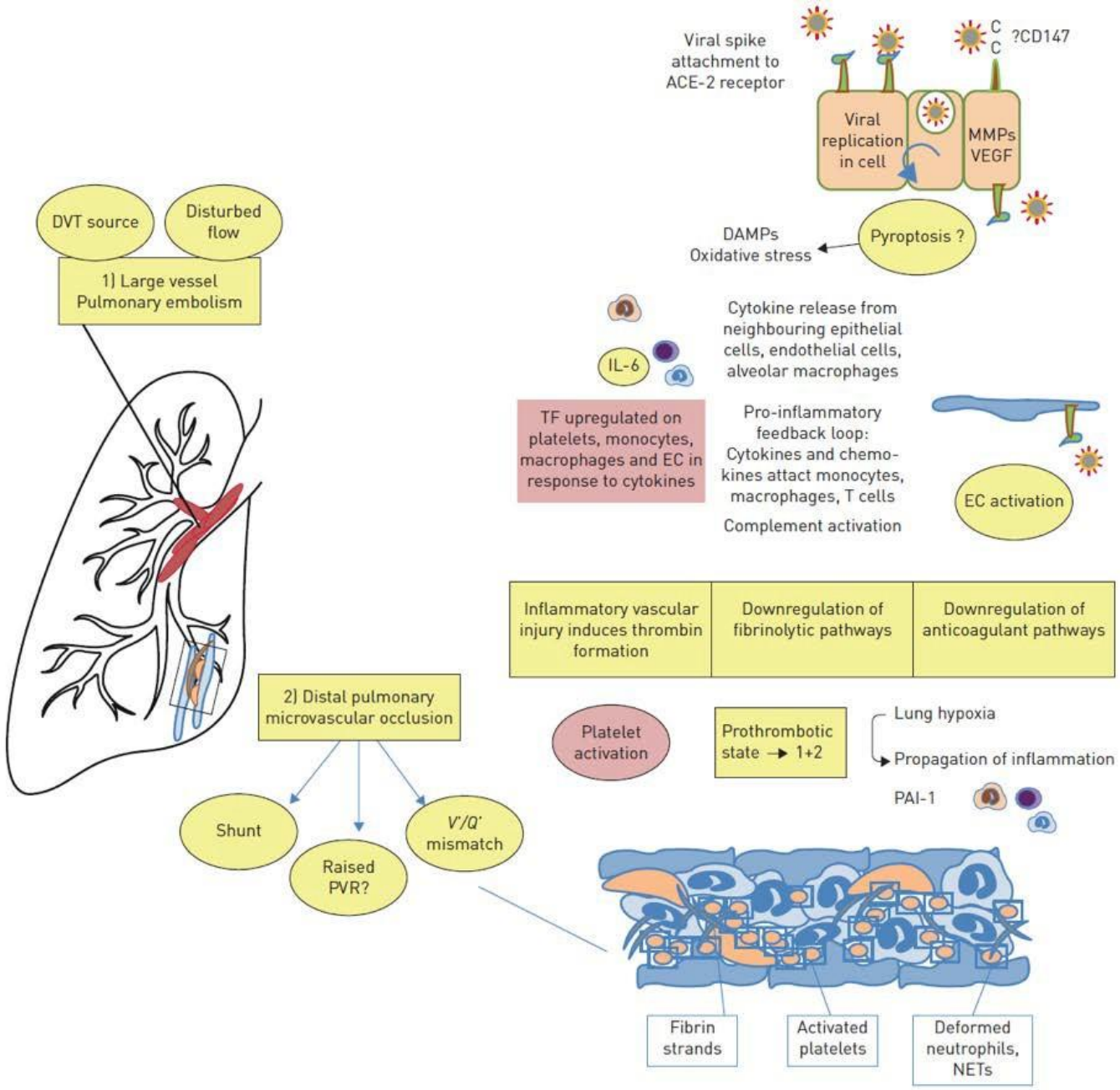
Macroscopic autopsy findings

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).



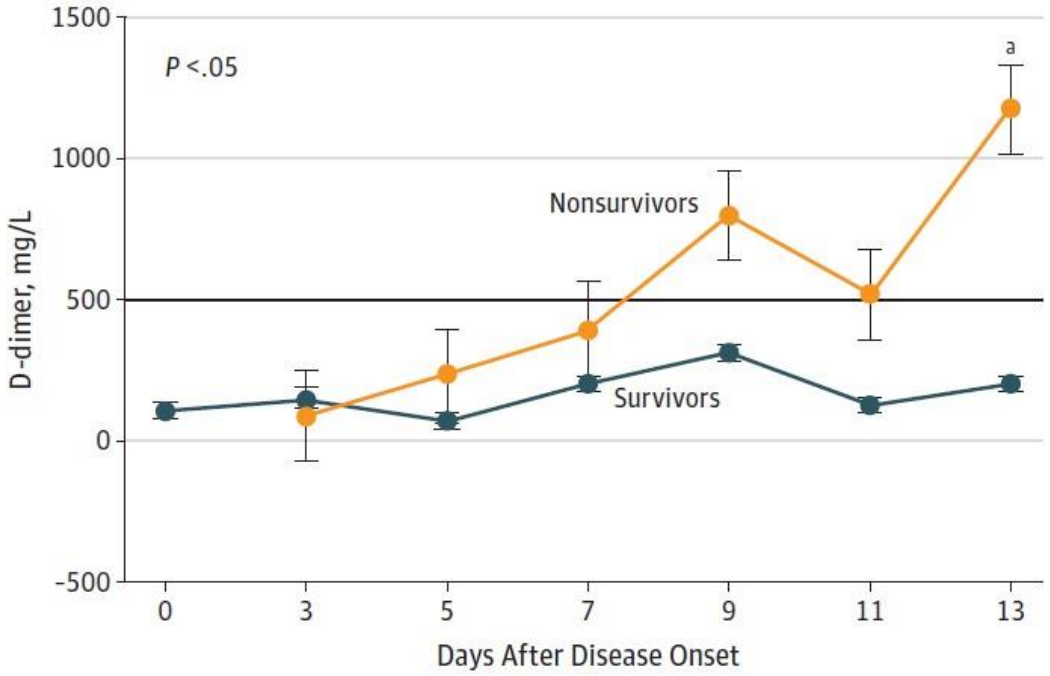
Wichmann D *et al*, Ann Int Med 2020

Pathophysiology of increased VTE risk

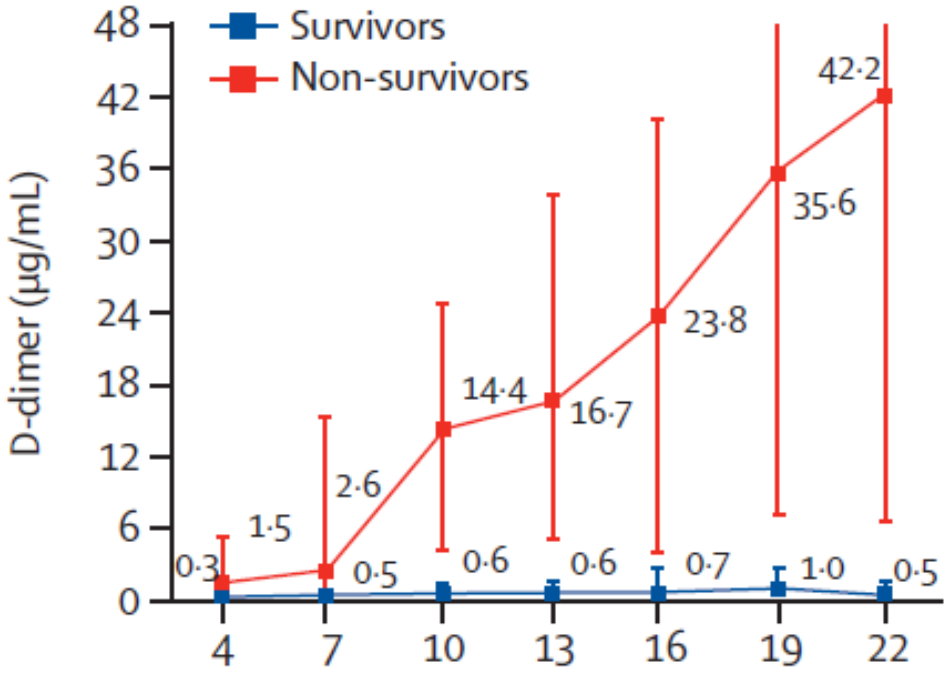


Price LC *et al*, Eur Respir J 2020

COVID-19 coagulopathy: initial reports (China)

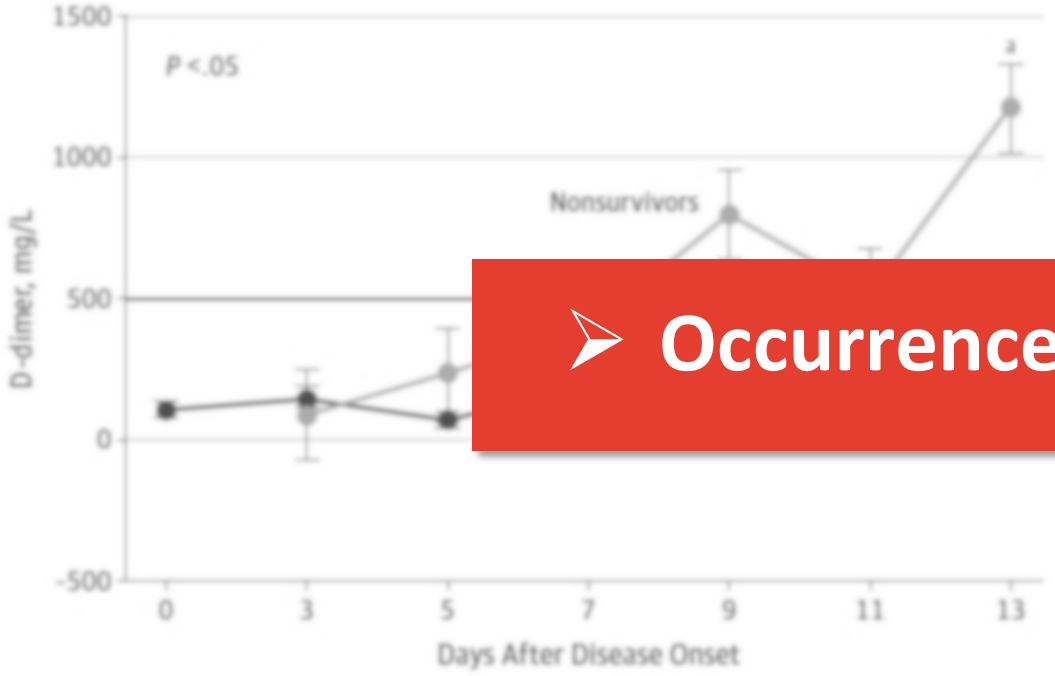


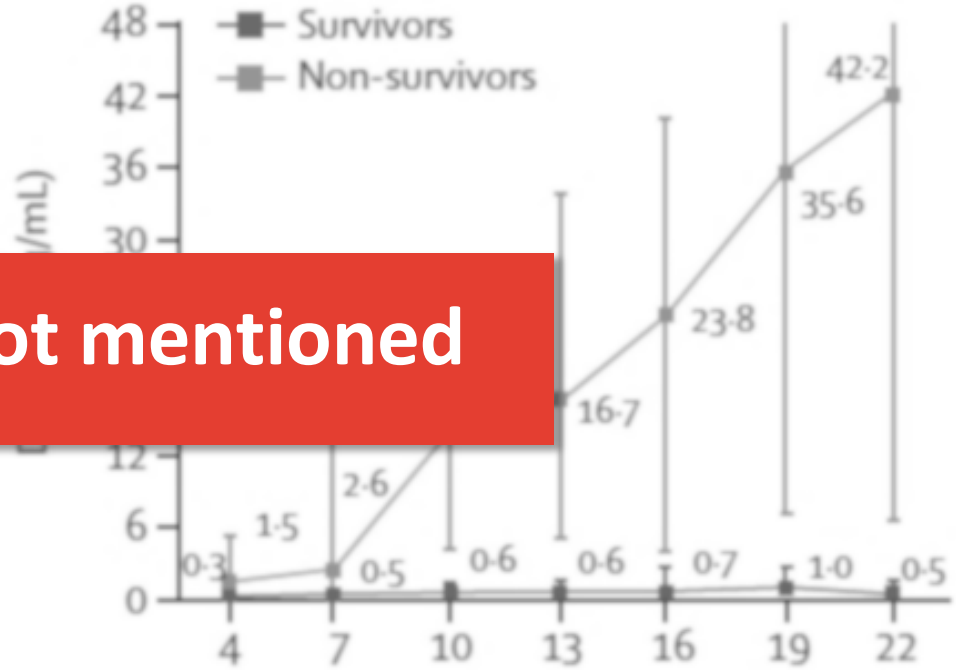
Wang D *et al*, JAMA 2020



Zhou F *et al*, Lancet 2020

COVID-19 coagulopathy: initial reports (China)



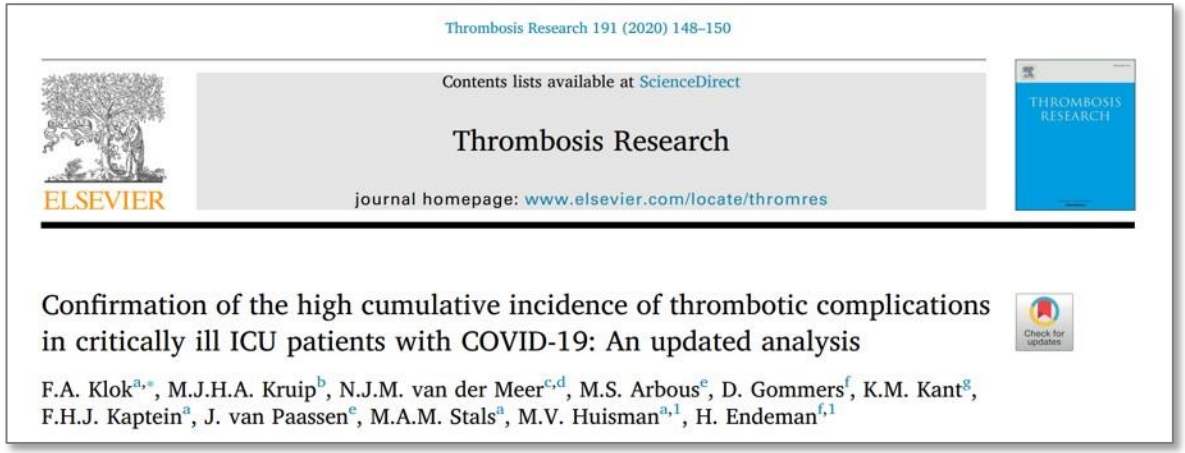


➢ **Occurrence of VTE not mentioned**

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

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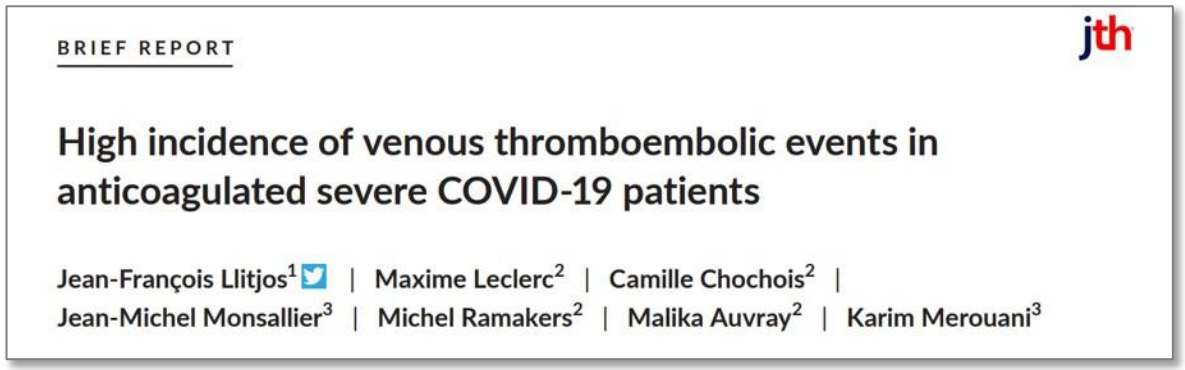
ELSEVIER

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]

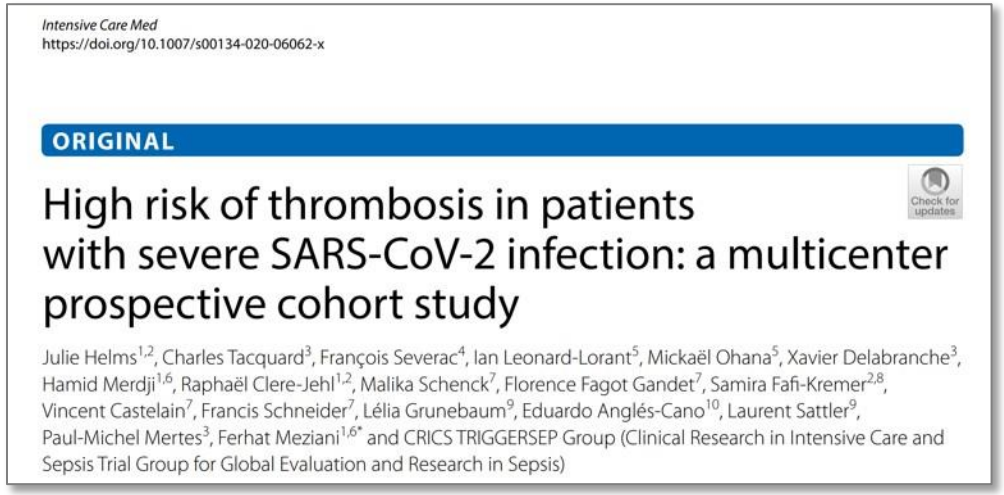


BRIEF REPORT

jth

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

Jean-François Llitjos[1] | Maxime Leclerc[2] | Camille Chochois[2] | Jean-Michel Monsallier[3] | Michel Ramakers[2] | Malika Auvray[2] | Karim Merouani[3]



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 Tacquard[3], François Severac[4], Ian Leonard-Lorant[5], Mickaël Ohana[5], Xavier Delabranche[3], Hamid Merdji[1,6], Raphaël Clere-Jehl[1,2], Malika Schenck[7], Florence Fagot Gandet[7], Samira Fafi-Kremer[2,8], Vincent Castelain[7], Francis Schneider[7], Lélia Grunebaum[9], Eduardo Anglés-Cano[10], Laurent Sattler[9], Paul-Michel Mertes[3], 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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ELSEVIER

Full Length Article

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

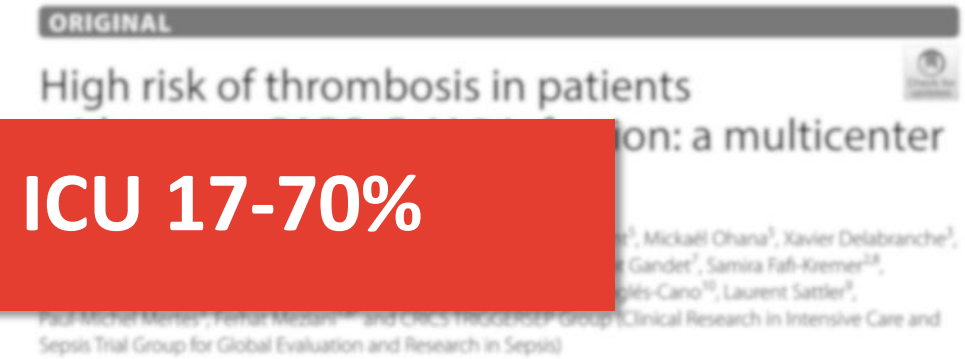
Corrado Lodigiani[a,b,*], Giacomo Iapichino[c], Luca Carenzo[c], Maurizio Cecconi[b,c], Paola Ferrazzi[a], Tim Sebastian[d], Nils Kucher[d], Jan-Dirk Studt[e], Clara Sacco[a], Bertuzzi Alexia[f], Maria Teresa Sandri[g], Stefano Barco[d,h], on behalf of the Humanitas COVID-19 Task Force

COVID-19 coagulopathy: initial reports (Europe)


Thrombosis Research

Confirmation of the high
in critically ill ICU patie

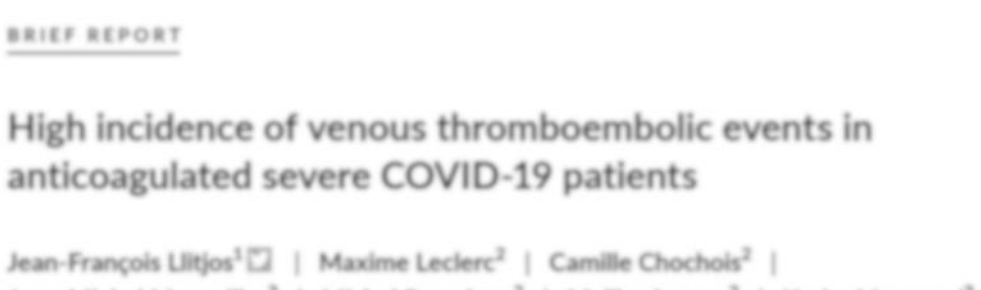
F.A. Klok, M.J.H.A. Kruip, F.H.J. Kaptein, J. van Paassen


ORIGINAL

High risk of thrombosis in patients
on: a multicenter

Mickaël Ohana, Xavier Delabranche, Gandet, Samira Fafi-Kremer, Laurent Sattler,
Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis)

- **Incidence of VTE in ICU 17-70%**


jth

BRIEF REPORT

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Thrombosis Research

Full Length Article

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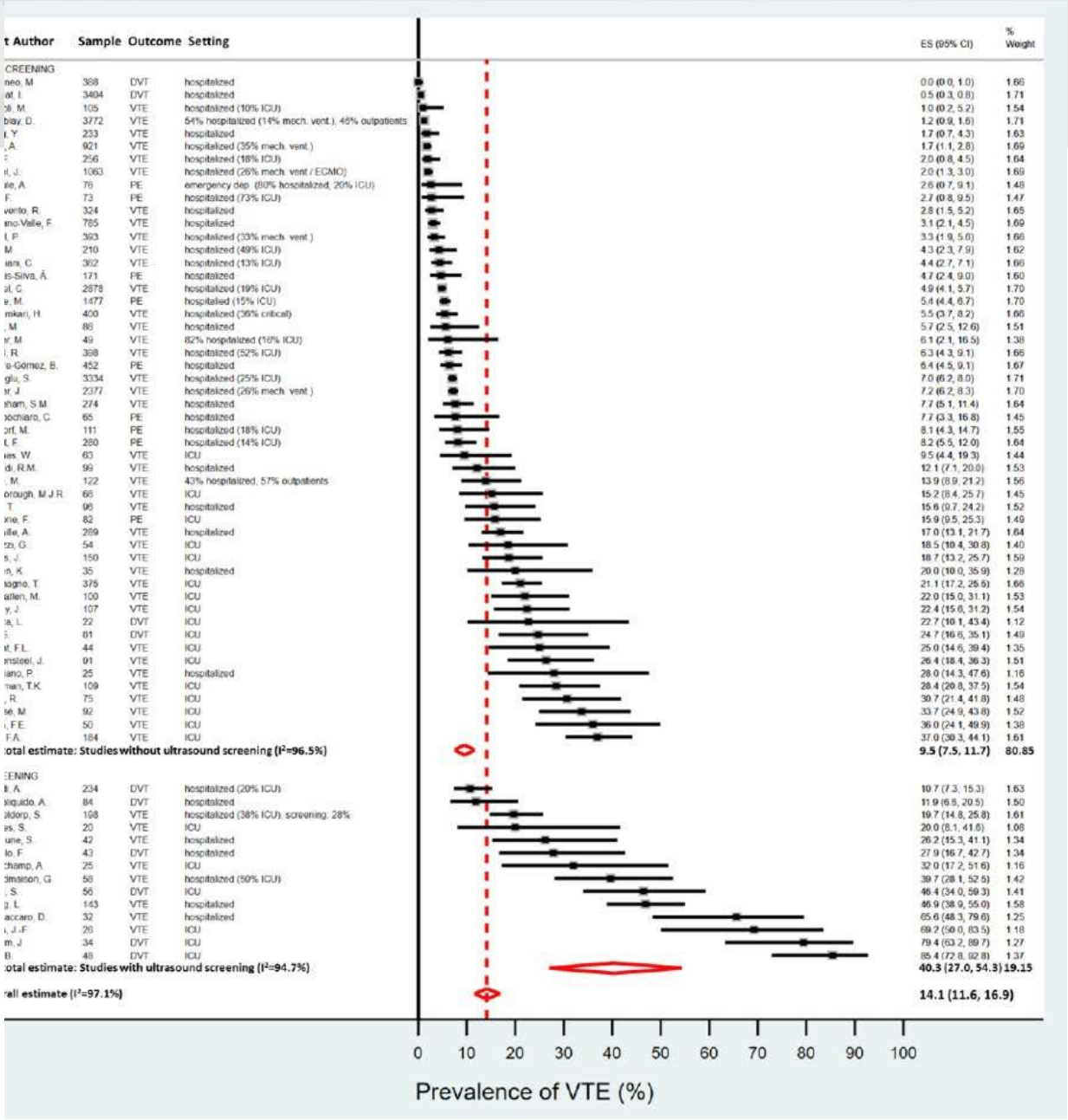
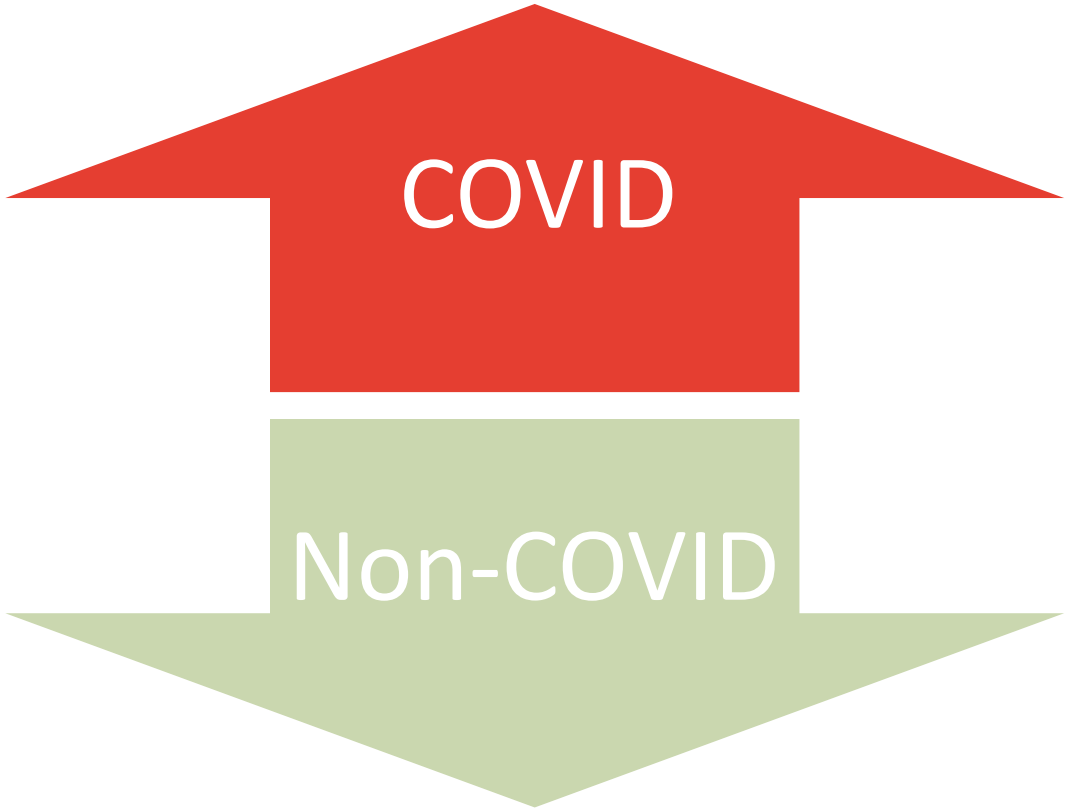
COVID-19: incidence of VTE

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



Nopp S *et al*, RPTH 2020

Precise rates of VTE were (are?) uncertain



Limitations

- Many small studies, few RCTs
- Most have high likelihood of bias
- Differences/challenges in diagnosis (e.g. screening vs. symptomatic)
- Definition of VTE (e.g. proximal vs. distal)
- Different prophylaxis strategies
- New variants and treatments over time

Blood Adv (2018) 2 (22): 3198–3225. Middeldorp et al, J Thromb Haemost 2020. Schunemann et al., Blood Adv 2018;2:3198-225. Cook et al, N Engl J Med 2011;364:1305-14.

Uncertainty of evidence = ongoing challenge

Evolving evidence over time highlights rationale for "living guideline"

Baseline risk studies

- Large number of studies (many low quality, few trials)
- Lack of definitions and/or descriptions of outcomes and measurement
- Incomplete/missing follow-up
- Uncertain baseline risk in 2024
- Disparities across populations

Effect of anticoagulation

- Confounding with use of different intensities in selected patients
- Lack of details regarding anticoagulant intensities
- Pragmatic open-label trial design (co-interventions)
- Uncertain benefit/harm in 2024

Individualized assessment of thrombosis and bleeding

Beneficial non-anticoagulant mechanisms?

Reduces viral entry to host cells

Reduces NET formation

Inhibits heparanase

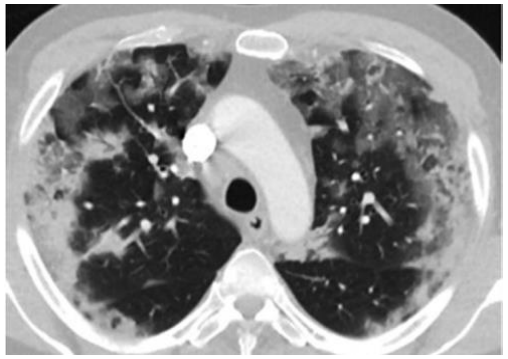
Intensive anticoagulant therapy beneficial?

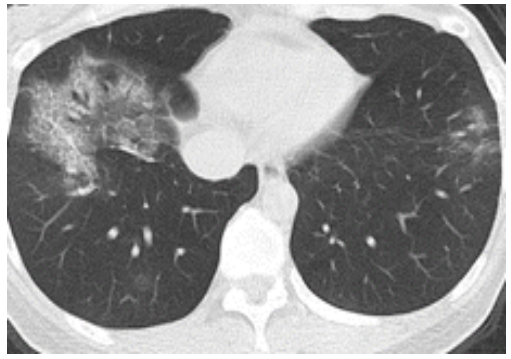
- High incidence of VTE
- Beneficial non-anticoagulant mechanisms (?)

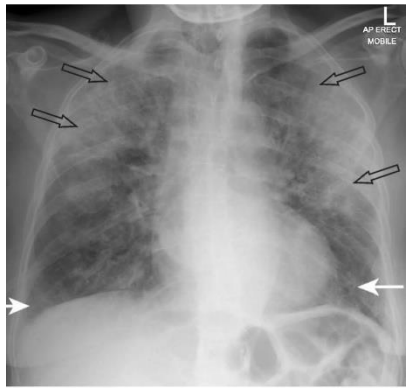
- Immunothrombosis
- Overdiagnosis of VTE (?)

Case Presentations

Patient T	Patient K	Patient X
♂, Chinese, 73 years	♂, White, 52 years	♀, Black, 68 years
BMI 34 kg/m^2, DM, hypertension	BMI 23 kg/m^2, Asthma	BMI 31 kg/m^2, rheumatoid arthritis
COVID-19 day 10	COVID-19 day 6	COVID-19 day 10
High fever, dyspneic at rest	Anosmia, shortness of breath with exercise	Hospitalized x 6 days, supplemental oxygen by nasal cannula, remdesivir
HR 123/min, RR 42/min, Sat 83% at 15L O2	HR 95/min, RR 20/min, sat 90% at room air	Off oxygen, mobilizing well





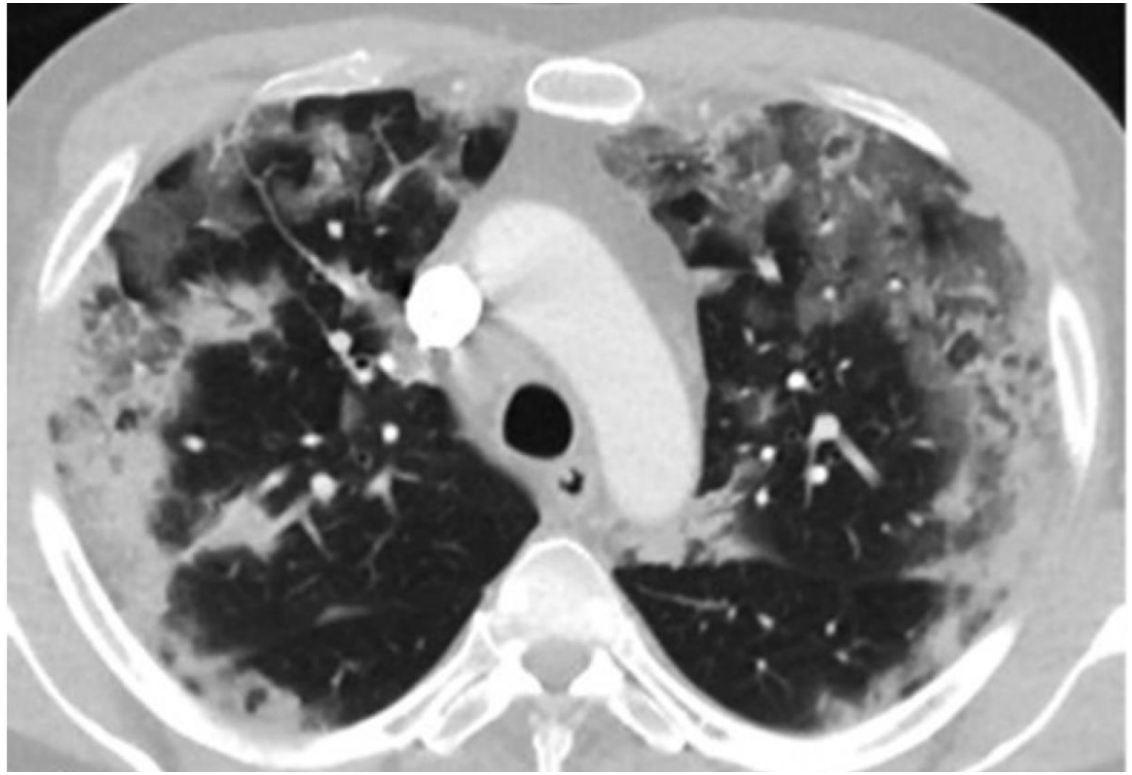


Million Dollar Question

What would be the optimal anticoagulant strategy in these 3 patients?

Case 1: COVID-19 Related Critical Illness

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 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

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 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 ***critical illness*** who do not have suspected or confirmed VTE
INTERVENTION:	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at intermediate-intensity
COMPARISON:	Prophylactic-intensity
MAIN OUTCOMES:	Mortality; Pulmonary embolism; Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT); Major bleeding; Multiple Organ Failure; Ischemic stroke (severe); Intracranial hemorrhage; Invasive mechanical ventilation; Limb amputation; ST-elevation myocardial infarction; Length of hospital admission; Length of ICU admission;

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with Prophylactic intensity	Risk with DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at intermediate-intensity
MORTALITY follow up: range 7 days to 30 days	891 (3 RCTs)	●○○○ VERY LOW	OR 0.92 (0.62 to 1.37)	278 per 1,000	16 fewer per 1,000 (from 85 fewer to 67 more)
PE follow up: range 7 days to 30 days	891 (3 RCTs)	●○○○ VERY LOW	OR 0.55 (0.12 to 2.62)	78 per 1,000	34 fewer per 1,000 (from 68 fewer to 103 more)
PROXIMAL LOWER EXTREMITY DVT follow up: range 7 days to 30 days	891 (3 RCTs)	●○○○ VERY LOW	OR 0.93 (0.23 to 3.80)	41 per 1,000	3 fewer per 1,000 (from 31 fewer to 99 more)
MAJOR BLEEDING follow up: range 7 days to 30 days	891 (3 RCTs)	●●○○ LOW	OR 1.50 (0.63 to 3.58)	34 per 1,000	16 more per 1,000 (from 12 fewer to 78 more)

Should DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at 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 ***critical illness*** who do not have suspected or confirmed VTE
INTERVENTION:	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity
COMPARISON:	Prophylactic-intensity
MAIN OUTCOMES:	Mortality; Pulmonary embolism; Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT); Major bleeding; Multiple Organ Failure; Ischemic stroke (severe); Intracranial hemorrhage; Invasive mechanical ventilation; Limb amputation; ST-elevation myocardial infarction; Length of hospital admission; Length of ICU admission;

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with Prophylactic intensity	Risk with DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at intermediate-intensity
MORTALITY follow up: range 7 days to 30 days	1951 (7 RCTs)	●○○○ VERY LOW	OR 0.90 (0.70 to 1.17)	278 per 1,000	21 fewer per 1000 (from 66 fewer to 33 more)
PE follow up: range 7 days to 30 days	1942 (7 RCTs)	●○○○ VERY LOW	OR 0.40 (0.26 to 0.61)	78 per 1,000	45 fewer per 1000 (from 56 fewer to 29 fewer)
PROXIMAL LOWER EXTREMITY DVT follow up: range 7 days to 30 days	1942 (7 RCTs)	●○○○ VERY LOW	OR 0.73 (0.42 to 1.24)	41 per 1,000	11 fewer per 1000 (from 23 fewer to 9 more)
MAJOR BLEEDING follow up: range 7 days to 30 days	1944 (7 RCTs)	●●○○ LOW	OR 1.78 (1.00 to 3.18)	34 per 1,000	25 more per 1000 (from 0 fewer to 67 more)

Recommendation

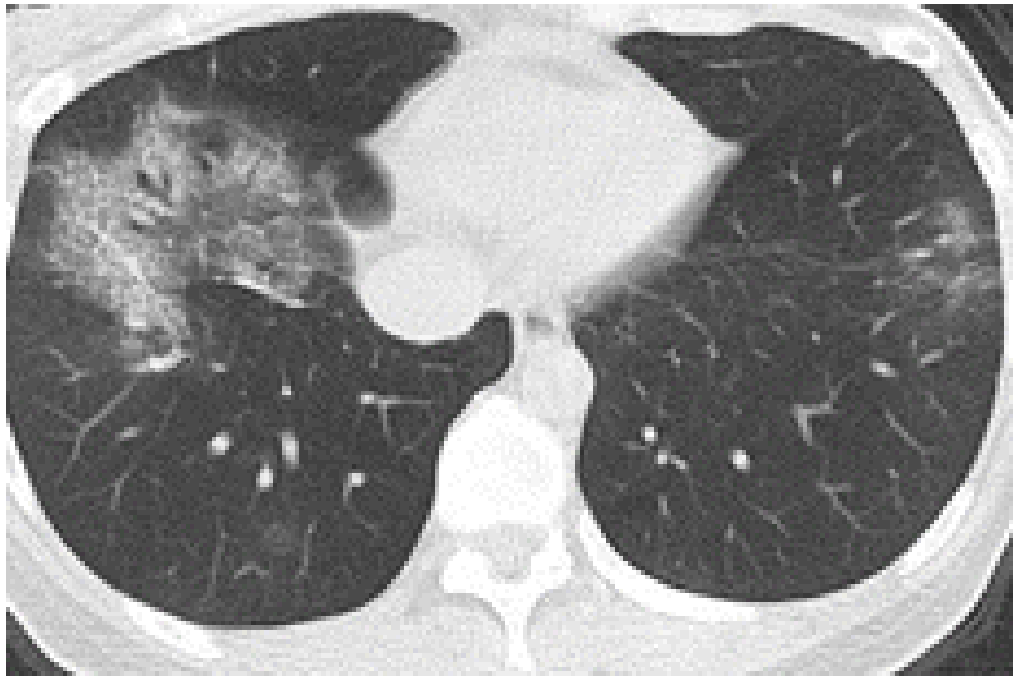
The ASH guideline panel suggests using prophylactic-intensity over intermediate- intensity or therapeutic-intensity anticoagulation in patients with COVID-19 related critical illness who do not have suspected or confirmed VTE
*(Conditional recommendation based on **very low certainty** in the evidence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



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

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 vs. Prophylactic-intensity be used for Patients with COVID-19 related acute illness who do not have suspected or confirmed VTE (PICO 2a)?

POPULATION:	Patients with COVID-19 related ***acute illness*** who do not have suspected or confirmed VTE
INTERVENTION:	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Intermediate-intensity
COMPARISON:	Prophylactic-intensity
MAIN OUTCOMES:	All-cause mortality; Pulmonary embolism - Moderate severity; Deep Venous Thrombosis of the upper leg - Moderate severity; Major bleeding; Multiple organ failure; Ischemic stroke - Severe; Intracranial hemorrhage; Invasive mechanical ventilation - Long-term; Limb amputation; ICU hospitalization; ST-elevation myocardial infarction

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-intensity
ALL-CAUSE MORTALITY follow-up: range 5 to 50 days	445 (3 RCTs)	●○○○ VERY LOW	OR 1.49 (0.82 to 2.72)	97 per 1,000	41 more per 1000 (from 16 fewer to 129 more)
PE follow-up: range 4 to 34 days	445 (3 RCTs)	●○○○ VERY LOW	OR 0.51 (0.10 to 2.67)	26 per 1,000	13 fewer per 1000 (from 23 fewer to 41 more)
PROXIMAL LOWER EXTREMITY DVT follow up: range 4 to 34 days	445 (3 RCTs)	●○○○ VERY LOW	not estimable	8 per 1,000	--
MAJOR BLEEDING follow up: range 5 to 30 days	445 (3 RCTs)	●○○○ VERY LOW	OR 1.01 (0.06 to 16.41)	13 per 1,000	0 fewer per 1000 (from 12 fewer to 165 more)
MULTIPLE ORGAN FAILURE follow up: mean 30 days	183 (1 RCT)	●○○○ VERY LOW	OR 1.53 (0.25 to 9.40)	49 per 1,000	24 more per 1000 (from 36 fewer to 277 more)

Should DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Therapeutic-intensity vs. Prophylactic-intensity be used for Patients with COVID-19 related acute illness who do not have suspected or confirmed VTE (PICO 2b)?

POPULATION:	Patients with COVID-19 related ***acute illness*** who do not have suspected or confirmed VTE
INTERVENTION:	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Therapeutic-intensity
COMPARISON:	Prophylactic-intensity
MAIN OUTCOMES:	All-cause mortality; Pulmonary embolism - Moderate severity; Deep Venous Thrombosis of the upper leg - Moderate severity; Major bleeding; Multiple organ failure; Ischemic stroke - Severe; Intracranial hemorrhage; Invasive mechanical ventilation - Long-term; Limb amputation; ICU hospitalization; ST-elevation myocardial infarction;

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 therapeutic-intensity
ALL-CAUSE MORTALITY follow-up: range 5 to 50 days	7287 (9 RCTs)	●●○○ LOW	OR 0.80 (0.55 to 1.16)	97 per 1,000	18 fewer per 1000 (from 41 fewer to 14 more)
PE follow-up: range 4 to 34 days	7085 (9 RCTs)	●●○○ LOW	OR 0.53 (0.33 to 0.83)	26 per 1,000	12 fewer per 1000 (from 17 fewer to 4 fewer)
PROXIMAL LOWER EXTREMITY DVT follow up: range 4 to 34 days	7085 (9 RCTs)	●●●○ MODERATE	OR 0.58 (0.30 to 1.08)	8 per 1,000	3 fewer per 1000 (from 6 fewer to 1 more)
MAJOR BLEEDING follow up: range 5 to 30 days	7295 (9 RCTs)	●●●○ MODERATE	OR 1.92 (1.10 to 3.36)	13 per 1,000	12 more per 1000 (from 1 more to 29 more)
MULTIPLE ORGAN FAILURE follow up: mean 30 days	700 (3 RCTs)	●○○○ VERY LOW	OR 0.46 (0.03 to 6.59)	49 per 1,000	26 fewer per 1000 (from 47 fewer to 204 more)

Recommendation

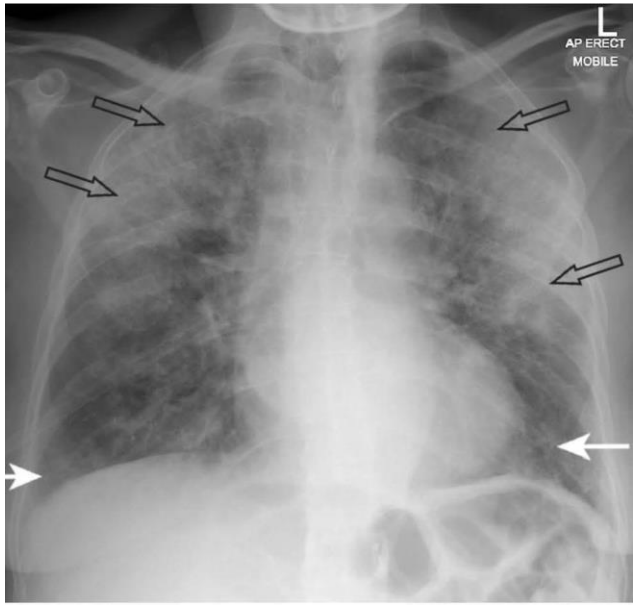
The guideline panel suggests using prophylactic-intensity over intermediate- intensity or therapeutic-intensity anticoagulation in patients with COVID-19 related acute illness who do not have suspected or confirmed VTE.
The ASH guideline panel suggests using prophylactic-intensity over intermediate- 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

Case 3: Discharge from hospital

Patient X
♀, Black, 68 years
BMI 31 kg/m^2, rheumatoid arthritis on methotrexate and TNF inhibitor
COVID-19 day 10
Hospitalized x 6 days, supplemental oxygen by nasal cannula, remdesivir
Off oxygen, mobilizing well



Cleverley et al. BMJ 2020;370:bmj.m2426

Question #3

Should prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux vs. no anticoagulation be used for post-discharge thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation?

Which ONE of the following options would you suggest for a patient with COVID-19 being discharged from the hospital and who does not have suspected or confirmed VTE or another indication for anticoagulation?

A. Intermediate- or therapeutic-intensity anticoagulation
B. No anticoagulation
C. Prophylactic-intensity anticoagulation
D. Aspirin

Which ONE of the following options would you suggest for a patient with COVID-19 being discharged from the hospital and who does not have suspected or confirmed VTE or another indication for anticoagulation?

A. Intermediate- or therapeutic-intensity anticoagulation

B. No anticoagulation

C. Prophylactic-intensity anticoagulation

D. Aspirin

Should prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux vs. no anticoagulation be used for post-discharge thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation?

POPULATION:	patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation
INTERVENTION:	prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux
COMPARISON:	No anticoagulation
MAIN OUTCOMES:	Mortality; Pulmonary Embolism; Deep Venous Thrombosis; Venous Thromboembolism; Major Bleeding; Ischemic Stroke; ST-elevation Myocardial Infarction; Readmission

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with no anticoagulation	Risk difference with anticoagulation at prophylactic-intensity
ALL-CAUSE MORTALITY follow up: range 6 to 90 days	1535 (2 RCTs)	●●○○ LOW	OR 0.84 (0.37 to 1.89)	19 per 1,000	3 fewer per 1000 (from 12 fewer to 16 more)
PE follow up: range 30 to 90 days	1535 (2 RCTs)	●●○○ LOW	OR 0.66 (0.08 to 5.44)	7 per 1,000	2 fewer per 1000 (from 6 fewer to 30 more)
PROXIMAL LOWER EXTREMITY DVT follow up: range 30 to 42 days	1535 (2 RCTs)	●●●○ MODERATE	OR 0.51 (0.08 to 3.29)	3 per 1,000	1 fewer per 1000 (from 3 fewer to 7 more)
MAJOR BLEEDING follow up: range 30 to 92 days	1535 (2 RCTs)	●●○○ LOW	OR 1.99 (0.18 to 22.04)	3 per 1,000	3 more per 1000 (from 2 fewer to 59 more)

Recommendation

The ASH guideline panel suggests against using outpatient anticoagulant thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation *(conditional recommendation based on very low certainty in the evidence about effects).*

The panel acknowledged that post-discharge thromboprophylaxis may be reasonable in patients judged to be at high thrombotic risk and low bleeding risk.

An individualized assessment of the patient's risk of thrombosis and bleeding and shared decision-making is important when deciding whether to use post-discharge thromboprophylaxis.

Very low certainty of evidence

Baseline risk studies

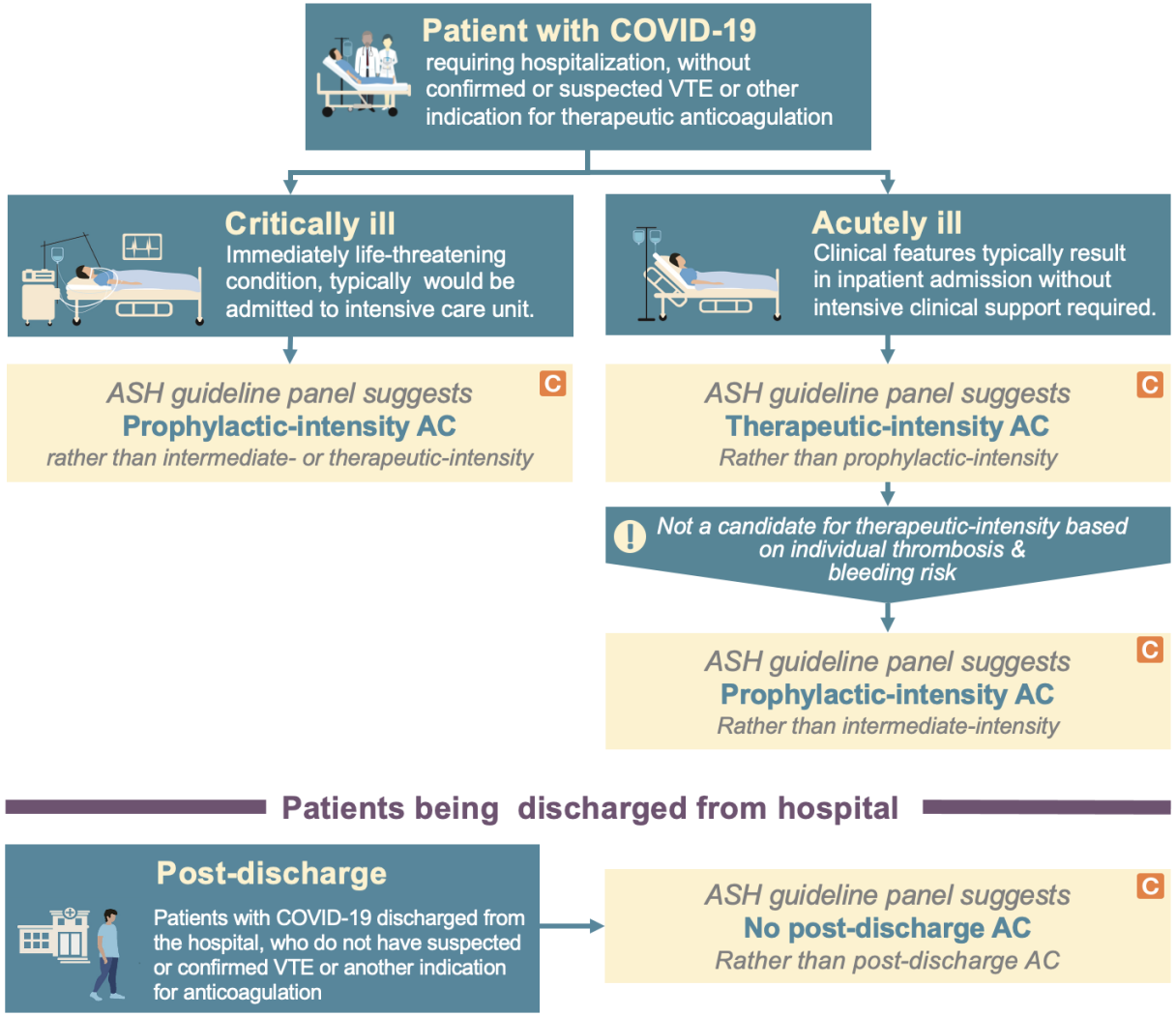
- Lack of definitions and/or descriptions of outcome measurement
- Incomplete/missing follow-up
- Incidence rates not reported (i.e. events per unit of follow-up)

Effect of anticoagulation studies

- Confounding with use of higher intensities in selected patients
- Lack of details regarding reported anticoagulant intensities

Putting it all together:

Executive summary and algorithm



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
3. Describe VTE prophylaxis recommendations for Patients who have been discharged after hospitalization for COVID-19 who do not have suspected or confirmed VTE
   - Post-discharge prophylactic intensity anticoagulation

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