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

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

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CLINICAL GUIDELINES

blood advances

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

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.

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*A.C. and E.K.T. are joint first authors.

The full-text version of this article contains a data supplement.

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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

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GRADEpro

Formulate question

P
I
C
O

Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important

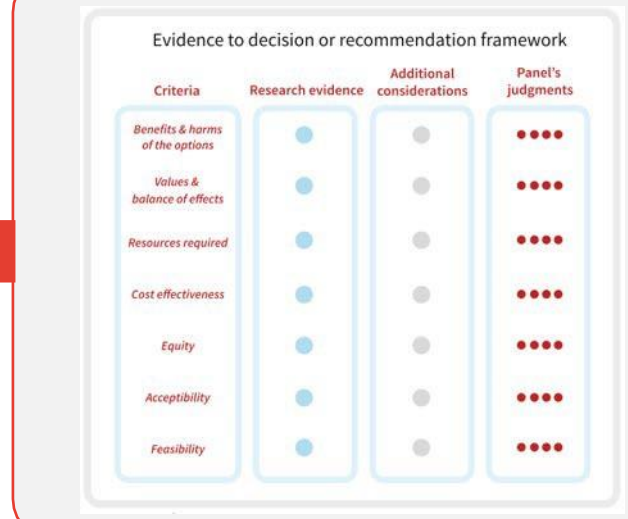
Assess single studies

Synthesize and Create

evidence profile & Evidence to Decision Table with GRADEpro

Rate certainty

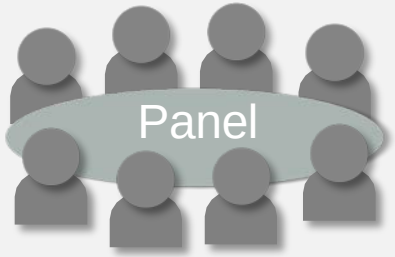
of evidence for each outcome and other criteria



Grade recommendations

(Evidence to Recommendation)

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



Recommendation/Decision

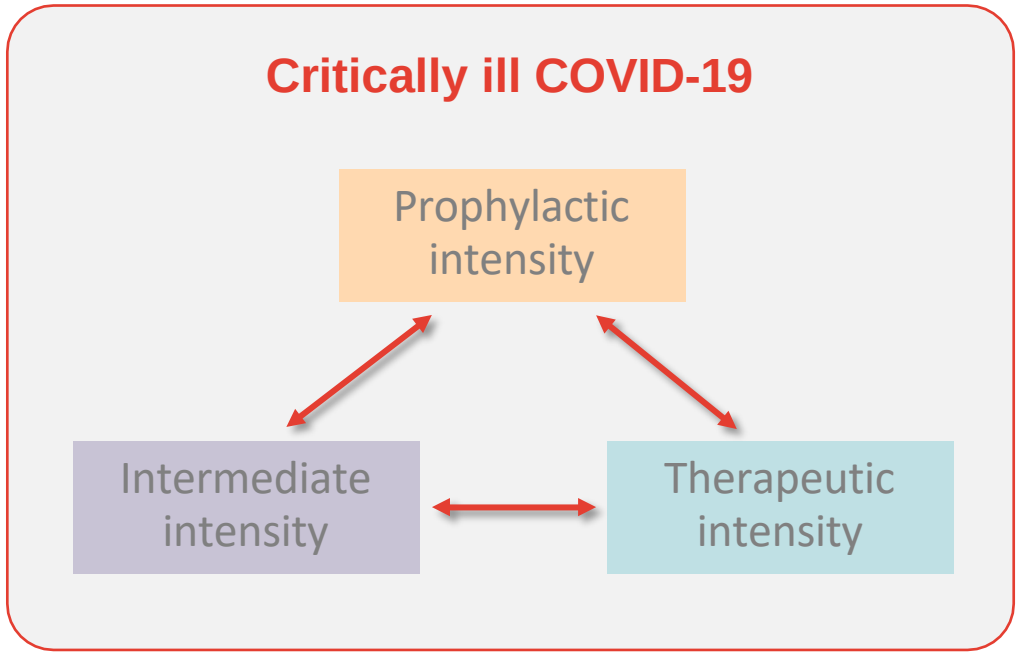
Guideline/coverage decision

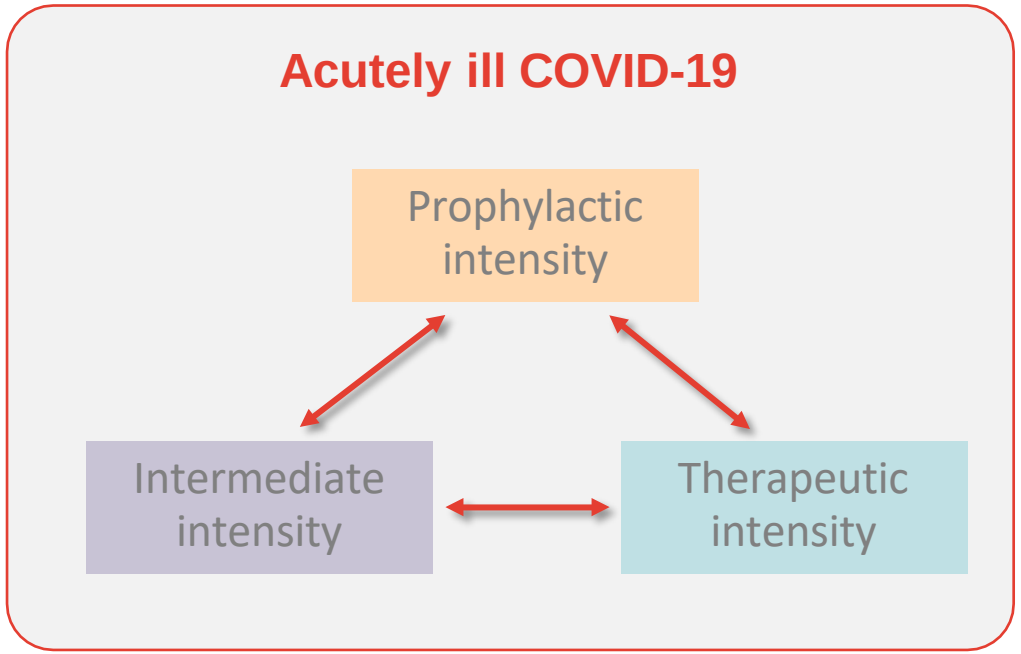
Evidence synthesis

(systematic review/HTA)

PICO Question Generation & Prioritization

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





Outcome Selection

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

Critical Outcomes

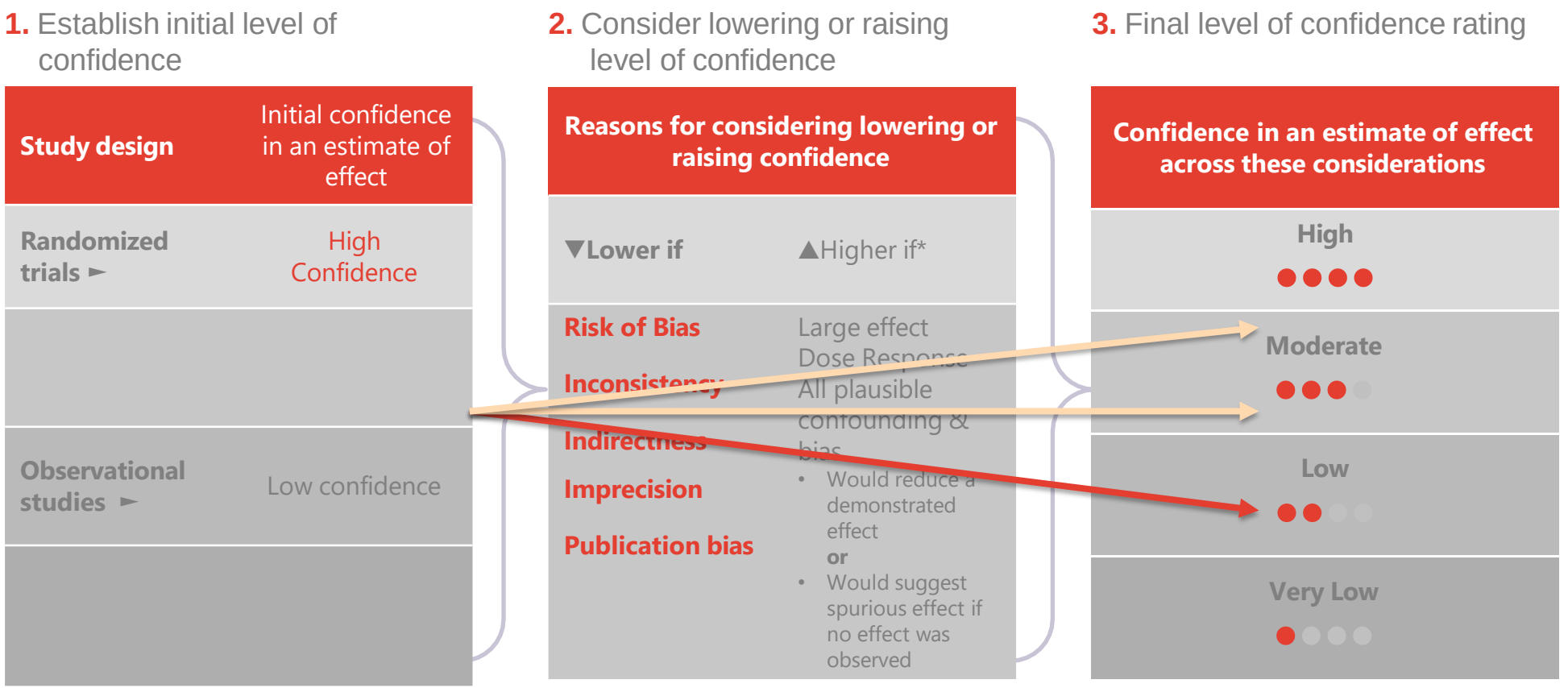
- All-cause mortality
- Pulmonary embolism
- Deep venous thrombosis
- Major bleeding
- Multi-organ failure
- Ischemic stroke
- Intracranial hemorrhage/hemorrhagic stroke
- Invasive mechanical ventilation
- Limb amputation
- ICU admission
- ST-elevation myocardial infarction

Evidence for Effect of the Intervention

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

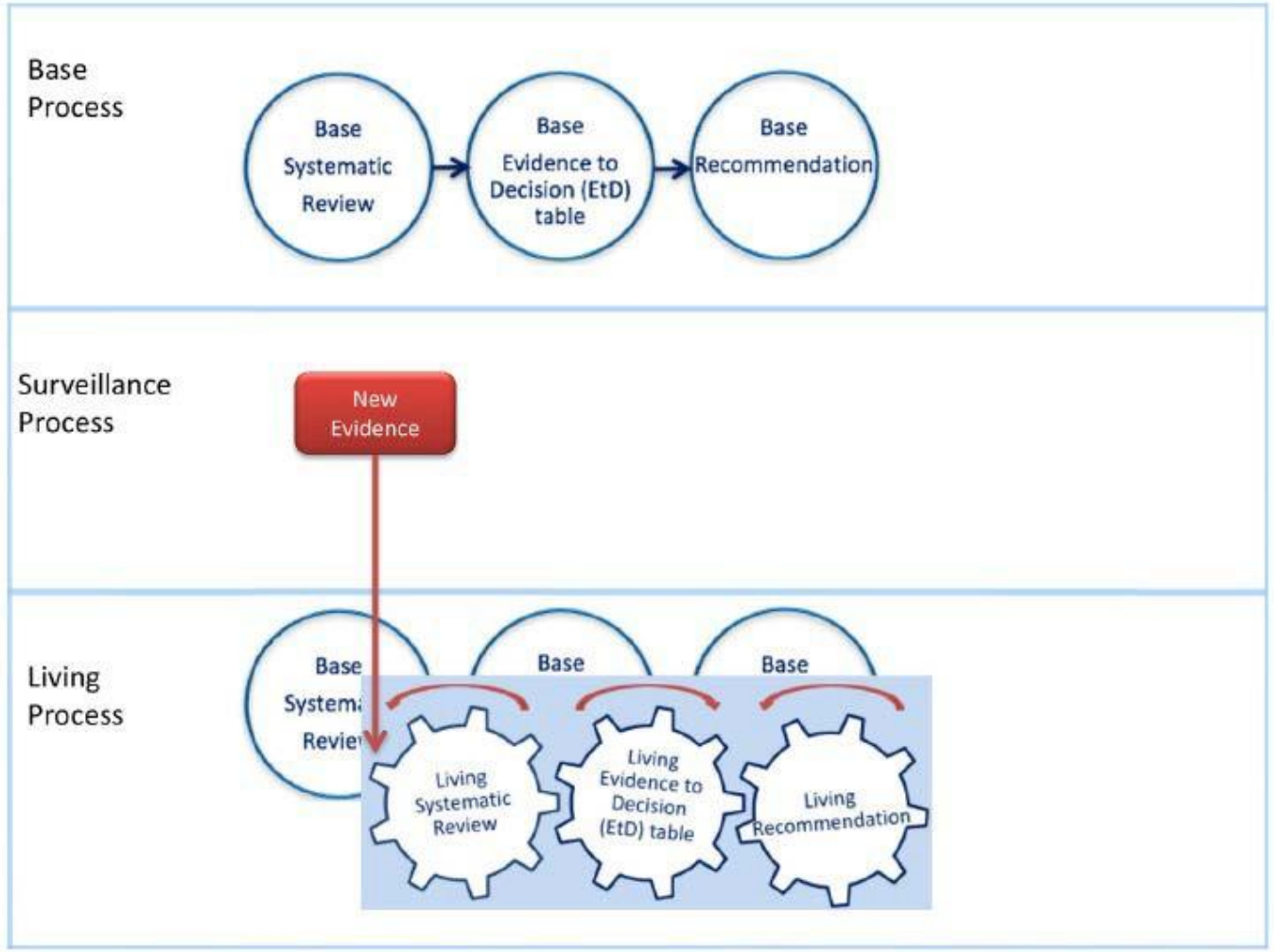


Fig. 2. The main steps of the living guideline process, focused on the unit of update, that is, the living recommendation.

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

Main Challenges

Evidence

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

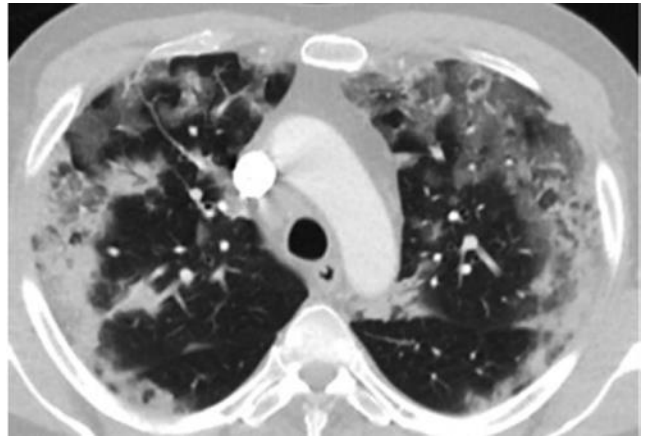
Recommendation formulation process

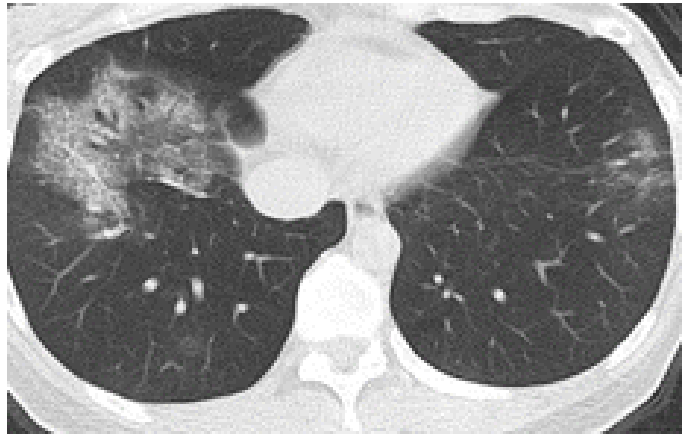
- Very low certainty evidence
- Not relying on non-COVID-19 evidence
- Criteria to reconsider recommendations with important new evidence in Living phase
- Provide timely and stable guidance

Case Presentations

Patient T
♂, Chinese, 73 years
BMI 34 kg/m^2, 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/m^2, Asthma
COVID-19 day 6
Anosmia, shortness of breath with exercise
HR 95/min, RR 20/min, sat 90% at room air





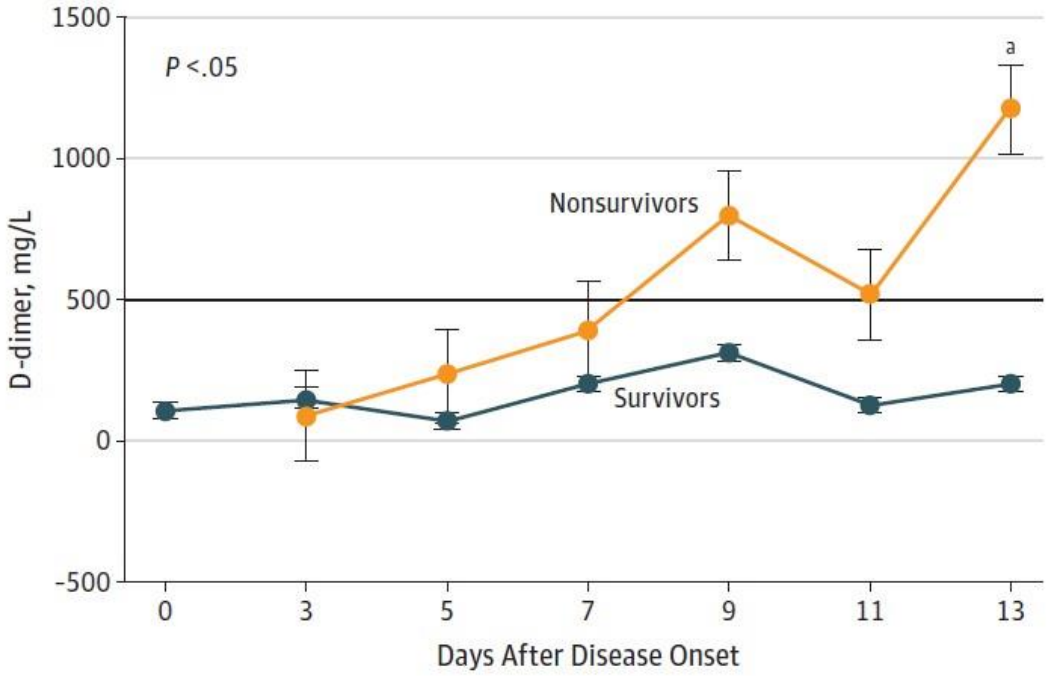
Million Dollar Question

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

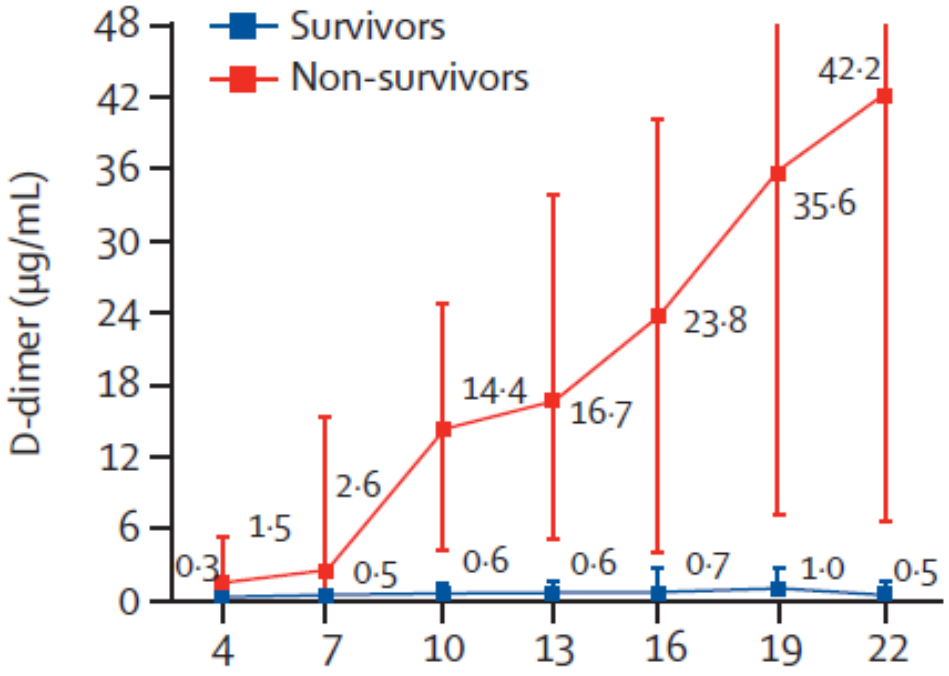
Which ONE of the following options would you suggest for thromboprophylaxis during this medical inpatient's hospital admission?

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)

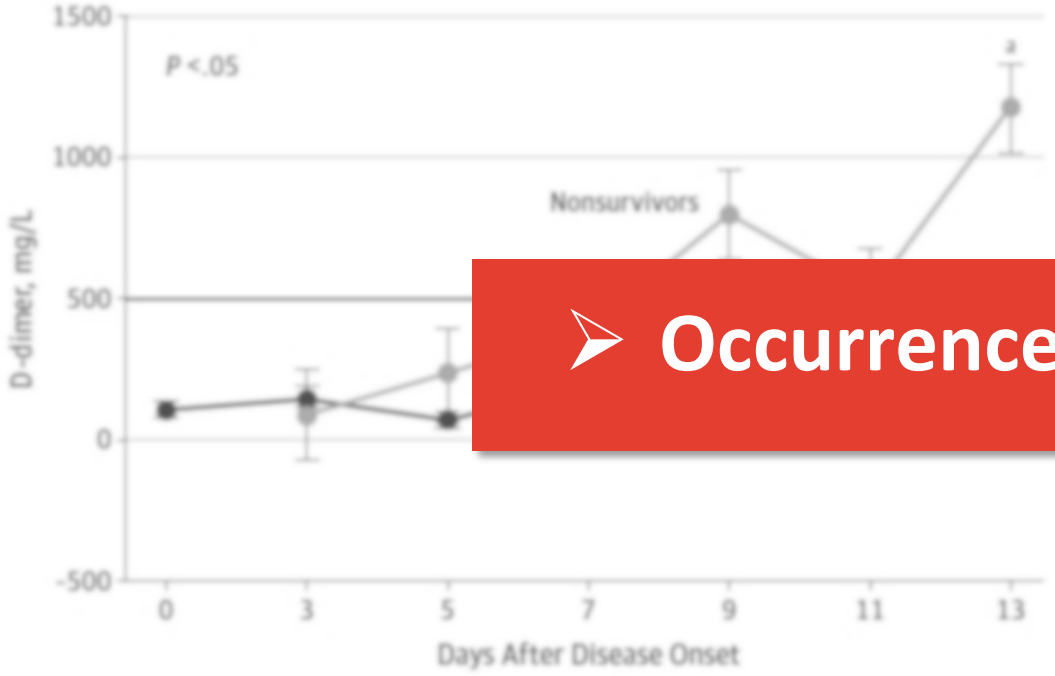


Wang D *et al*, JAMA 2020



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

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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]

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)

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]

Thrombosis Research 191 (2020) 9–14

Contents lists available at ScienceDirect

Thrombosis Research

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Full Length Article

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

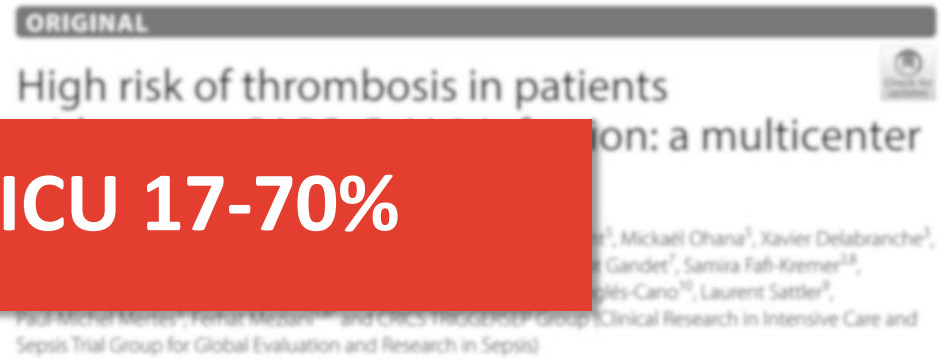
Corrado Lodigiani[a,b,*], Giacomo Iapichino[c], Luca Carenzo[c], Maurizio Cecconi[b,c], Paola Ferrazzi[a], Tim Sebastian[d], Nils Kucher[d], Jan-Dirk Studt[e], Clara Sacco[a], Bertuzzi Alexia[f], Maria Teresa Sandri[g], Stefano Barco[d,h], on behalf of the Humanitas COVID-19 Task Force

COVID-19 coagulopathy: initial reports (Europe)


Thrombosis Research

Confirmation of the high
in critically ill ICU patie

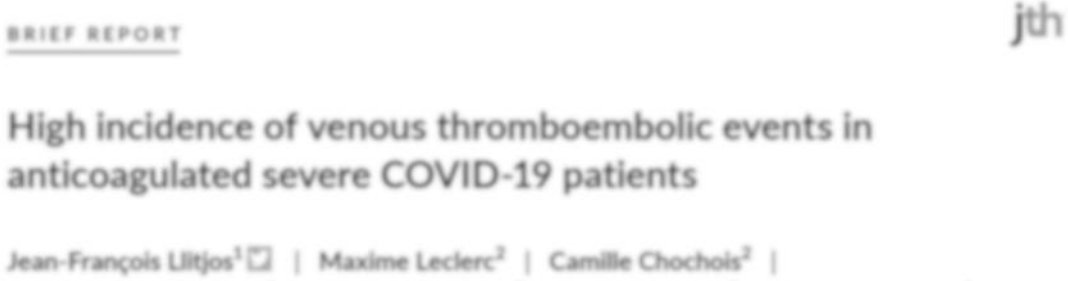
F.A. Klok, M.J.H.A. Kruip, N
F.H.J. Kaptein, J. van Paassen


ORIGINAL

High risk of thrombosis in patients
on: a multicenter

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

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


BRIEF REPORT

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Jean-François Llitjos | Maxime Leclerc | Camille Chochois |
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Thrombosis Research

Full Length Article

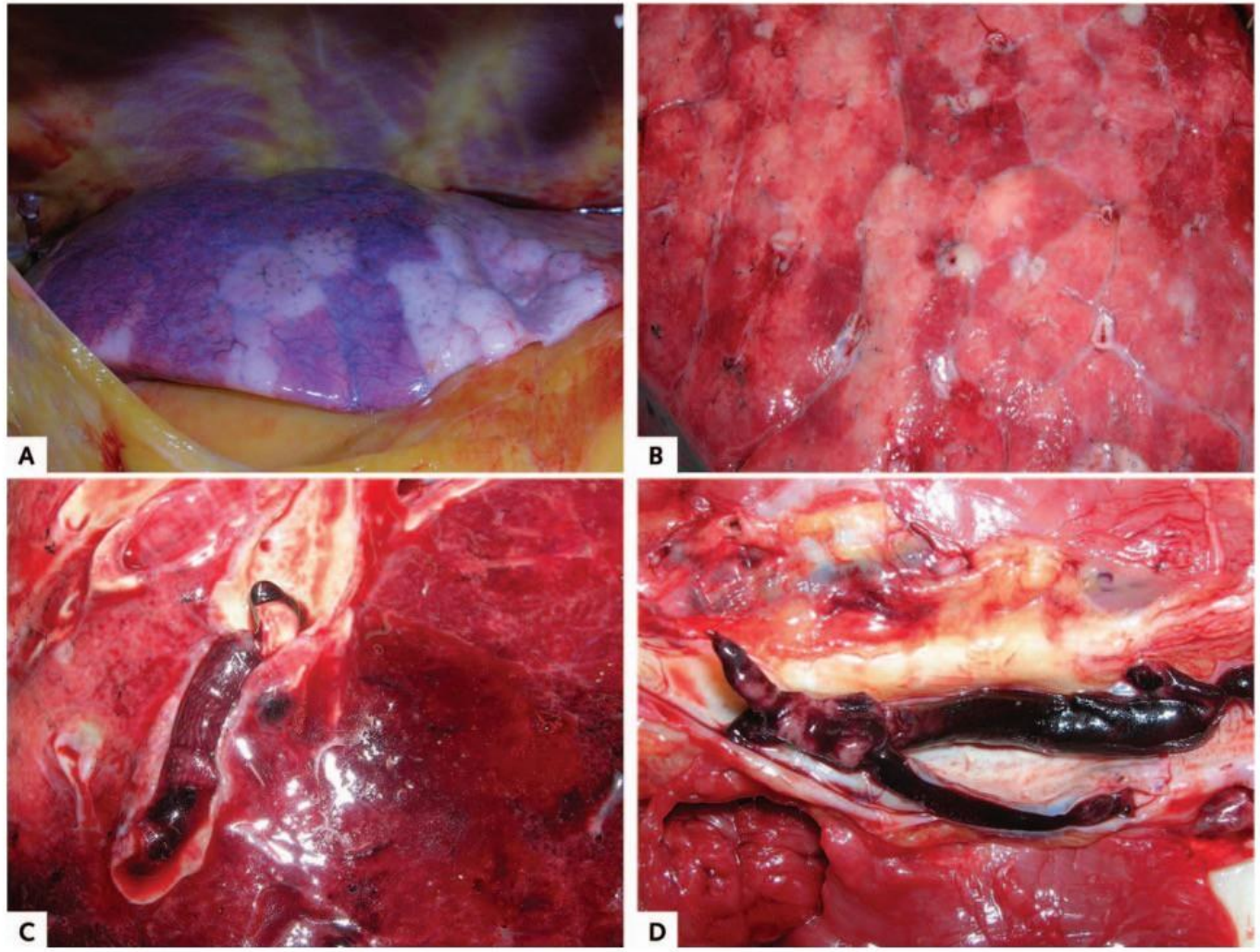
Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy

Corrado Lodigiani, Giacomo Iapichino, Luca Carenzo, Maurizio Cecconi, Paola Ferrazzi,
Tim Sebastian, Nils Kucher, Jan-Dirk Studt, Clara Sacco, Bertuzzi Alexia,
Maria Teresa Sandri, Stefano Barco, on behalf of the Humanitas COVID-19 Task Force

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

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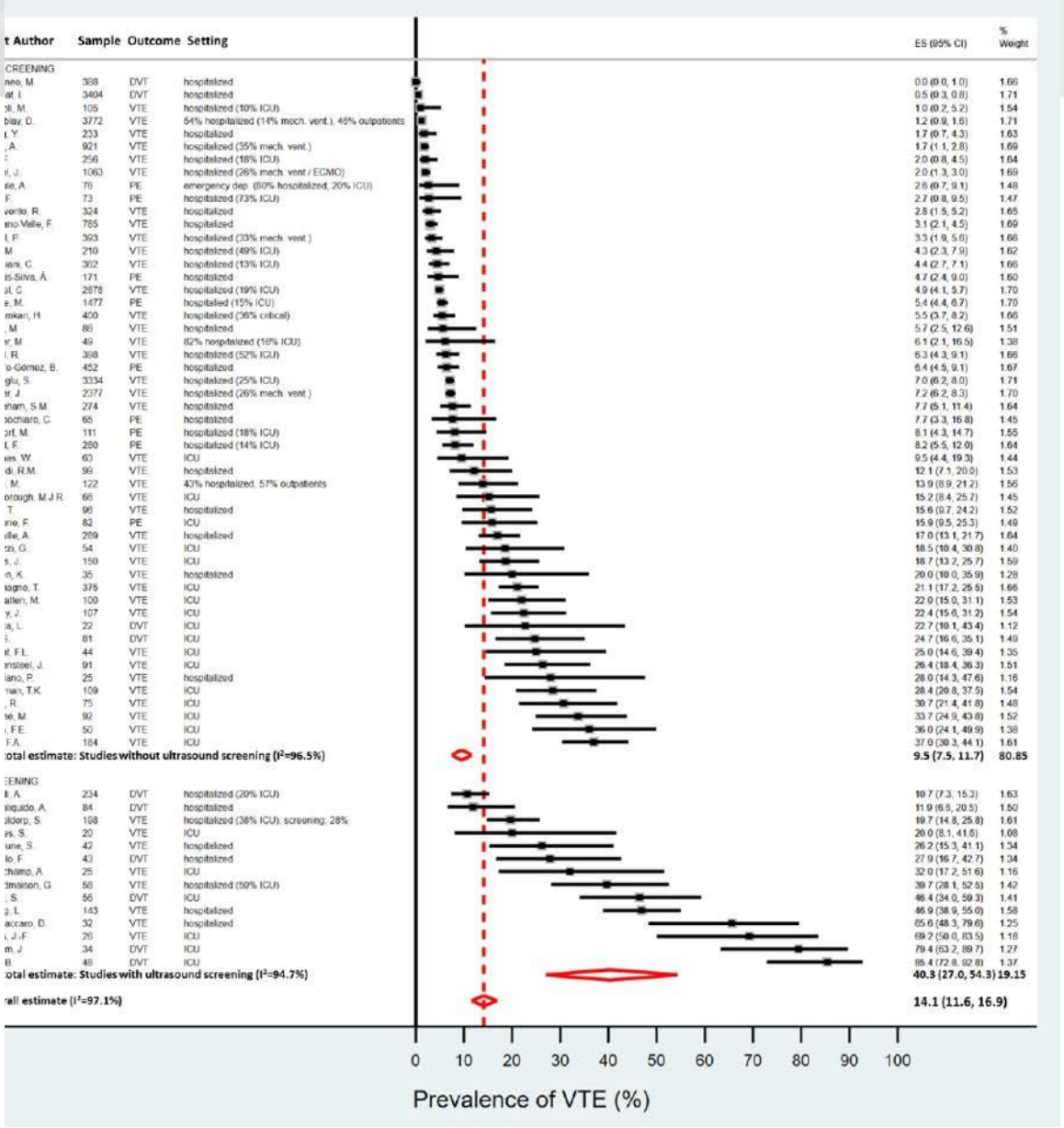
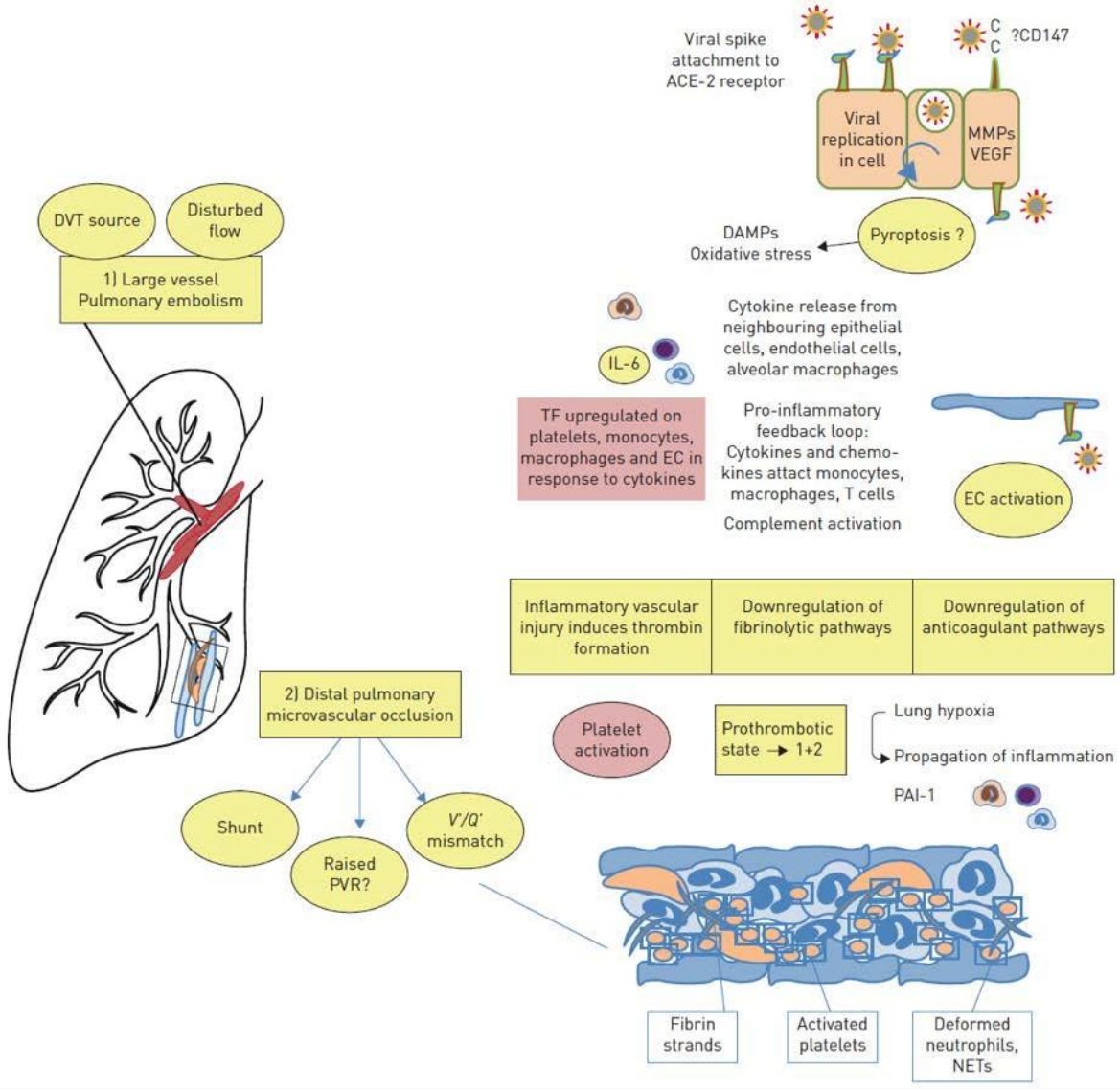
COVID-19: incidence of VTE

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



Nopp S *et al*, RPTH 2020

Pathophysiology of increased VTE risk



Price LC *et al*, Eur Respir J 2020

Beneficial non-anticoagulant mechanisms?

Reduces viral entry to host cells

Reduces NET formation

Inhibits heparanase

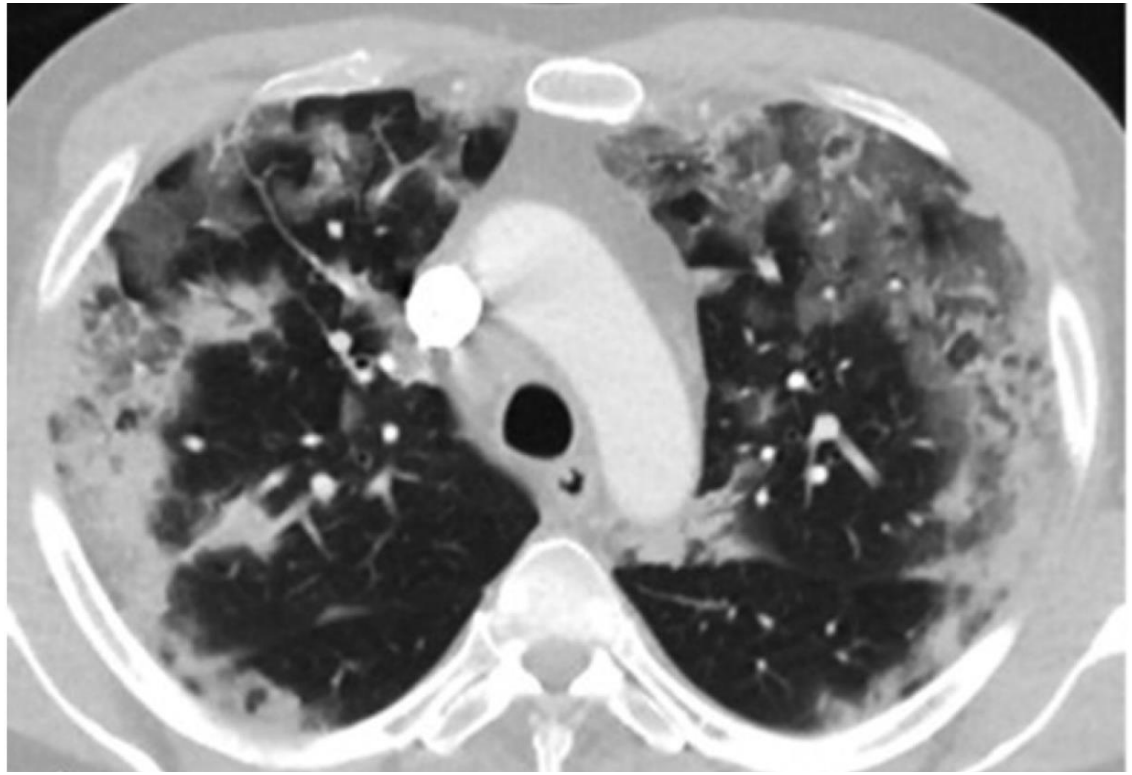
Intensive anticoagulant therapy beneficial?

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

- Immunothrombosis
- Overdiagnosis of VTE (?)

Case 1: COVID-19 Related Critical Illness

Patient T
♂, Chinese, 73 years
BMI 34 kg/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

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 ***critical illness*** who do not have suspected or confirmed VTE
INTERVENTION:	DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity
COMPARISON:	Prophylactic-intensity
MAIN OUTCOMES:	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	№ 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)

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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)
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Recommendation

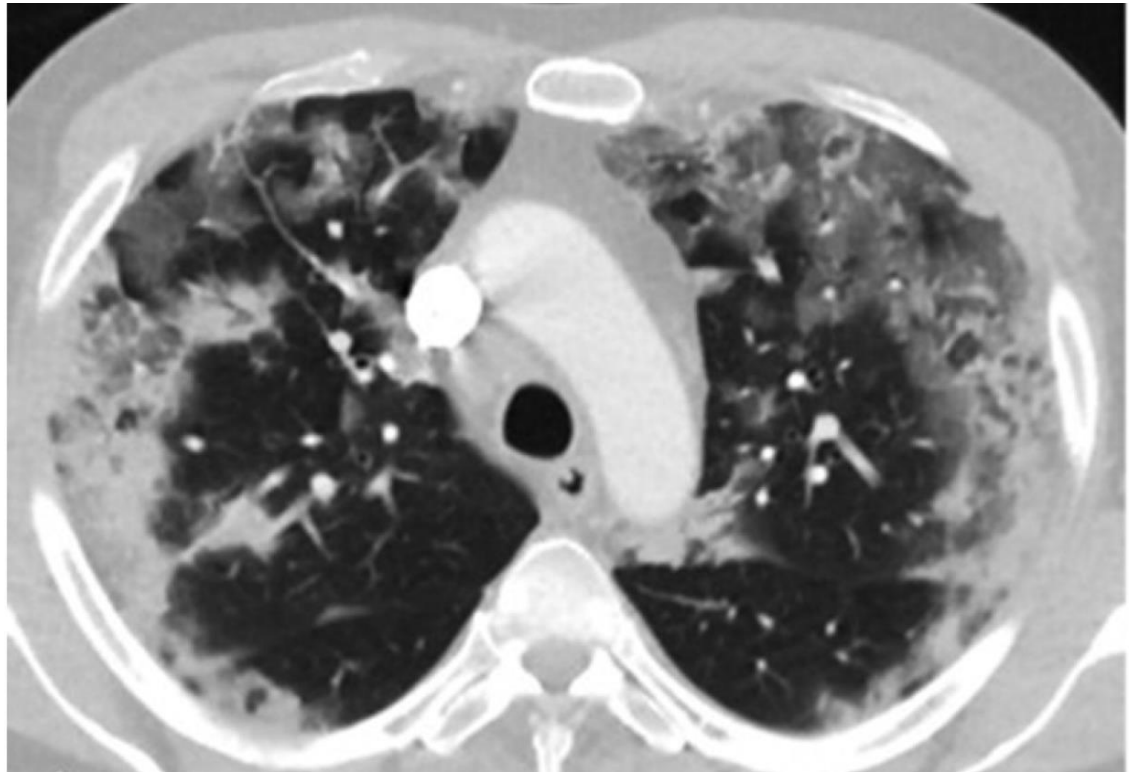
The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation in patients with COVID-19 related critical illness who do not have suspected or confirmed VTE *(Conditional recommendation based on **very low certainty** in the evidence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

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

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

Case 2: COVID-19 related acute illness

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

Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity vs. prophylactic-intensity be used for patients with COVID-19 related acute illness who do not have suspected or confirmed VTE?

POPULATION:	Patients with COVID-19 related ***acute illness*** who do not have suspected or confirmed VTE
INTERVENTION:	DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity
COMPARISON:	Prophylactic-intensity
MAIN OUTCOMES:	All-cause mortality; Pulmonary embolism; Proximal lower extremity DVT; Venous thromboembolism; Major bleeding; Multiple organ failure; Ischemic stroke; Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization; ST-elevation myocardial infarction;

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				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)	

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

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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