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Computable Evidence and Guidance to Support the Patient Journey

Stakeholder-driven “Art of the Possible” Patient Journeys for COVID-19 and Beyond

Session LB11

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Project Lead, EBMonFHIR; Project Lead, COVID-19 Knowledge Accelerator

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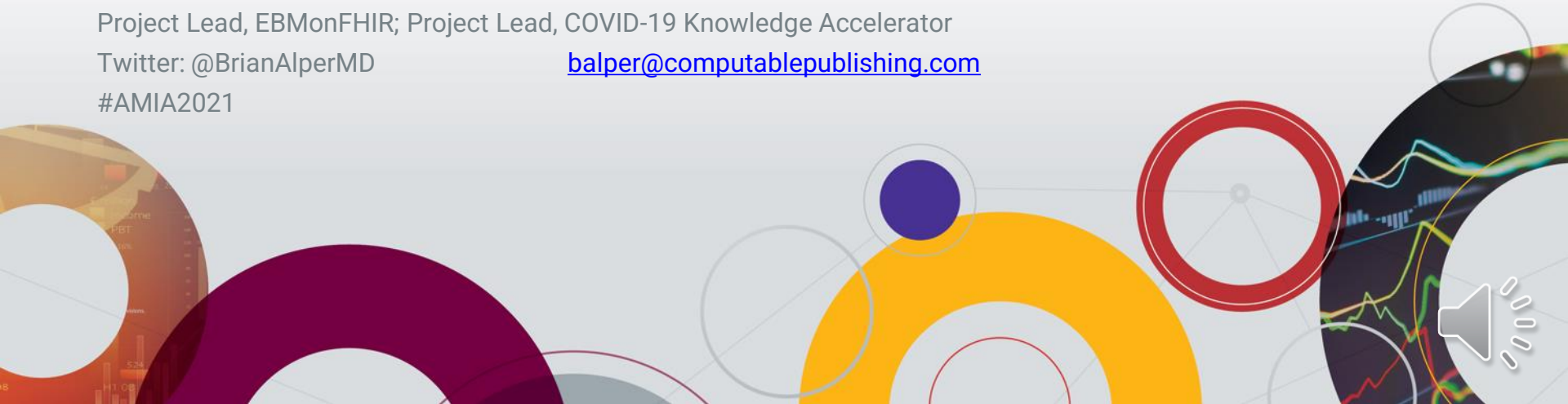


Disclosure

I disclose the following relevant relationship with commercial interests:

- Owner of Computable Publishing LLC

I disclose the following relevant relationships with non-commercial interests:

- President of Scientific Knowledge Accelerator Foundation
- Project Lead for COVID-19 Knowledge Accelerator
- Project Lead for EBMonFHIR (an HL7® project to extend HL7® FHIR® to support computable evidence and guidance)

Learning Objectives

After participating in this session, the learner should be better able to:

- Appreciate how computable evidence can improve the effectiveness, efficiency, and experience of the Patient Journey.
- Appreciate how computable guidance can improve the effectiveness, efficiency, and experience of the Patient Journey.
- Know how to participate in efforts to accelerate the knowledge transfer of scientific evidence and guidance through computerization.

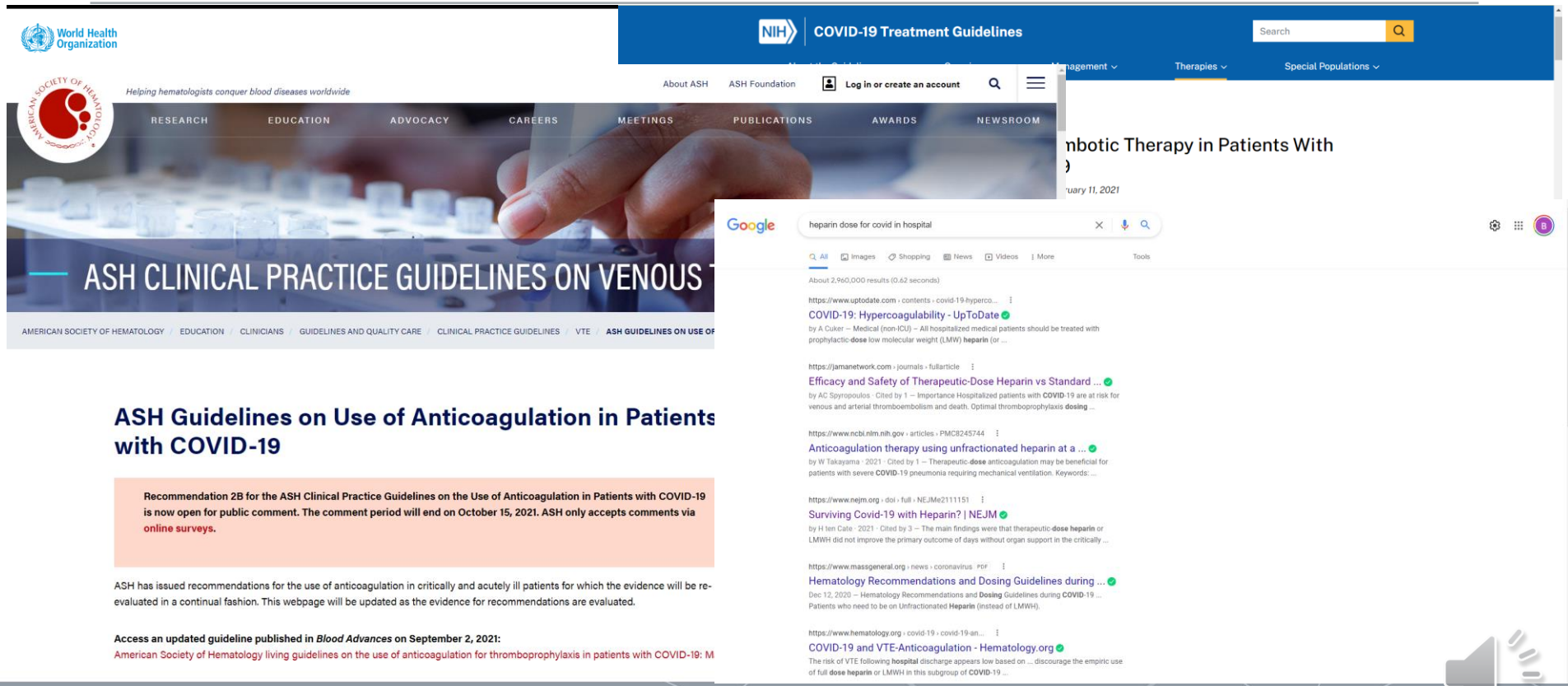
How much heparin for Mae?

Mae was just admitted to your hospital service due to a COVID-19 infection.

- Mae requires some oxygen support but luckily does not require mechanical ventilation.
- She is alert, conversant, pleasant, and does not seem stressed at being in the hospital. She can never take off from her role as primary caretaker for her granddaughter and jokes this is a forced vacation.
- She has no history of major bleeding or clotting problems.

You recently heard mixed messages about what doses of heparin you should use for patients hospitalized for COVID-19.

Who do I ask?


World Health Organization
Helping hematologists conquer blood diseases worldwide
About ASH
ASH Foundation
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AMERICAN SOCIETY OF HEMATOLOGY / EDUCATION / CLINICIANS / GUIDELINES AND QUALITY CARE / CLINICAL PRACTICE GUIDELINES / VTE / ASH GUIDELINES ON USE OF
ASH Guidelines on Use of Anticoagulation in Patients with COVID-19
Recommendation 2B for the ASH Clinical Practice Guidelines on the Use of Anticoagulation in Patients with COVID-19 is now open for public comment. The comment period will end on October 15, 2021. ASH only accepts comments via online surveys.
ASH has issued recommendations for the use of anticoagulation in critically and acutely ill patients for which the evidence will be re-evaluated in a continual fashion. This webpage will be updated as the evidence for recommendations are evaluated.
Access an updated guideline published in Blood Advances on September 2, 2021:
American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: M
NIH
COVID-19 Treatment Guidelines
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nbotic Therapy in Patients With
uary 11, 2021
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heparin dose for covid in hospital
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https://www.uptodate.com › contents › covid-19-hyperco...
COVID-19: Hypercoagulability - UpToDate
by A Cuker — Medical (non-ICU) – All hospitalized medical patients should be treated with prophylactic-dose low molecular weight (LMW) heparin (or ...
https://jamanetwork.com › journals › fullarticle
Efficacy and Safety of Therapeutic-Dose Heparin vs Standard ...
by AC Spyropoulos · Cited by 1 — Importance Hospitalized patients with COVID-19 are at risk for venous and arterial thromboembolism and death. Optimal thromboprophylaxis dosing ...
https://www.ncbi.nlm.nih.gov › articles › PMC8245744
Anticoagulation therapy using unfractionated heparin at a ...
by W Takayama · 2021 · Cited by 1 — Therapeutic-dose anticoagulation may be beneficial for patients with severe COVID-19 pneumonia requiring mechanical ventilation. Keywords: ...
https://www.nejm.org › doi › full › NEJMe2111151
Surviving Covid-19 with Heparin? | NEJM
by H ten Cate · 2021 · Cited by 3 — The main findings were that therapeutic-dose heparin or LMWH did not improve the primary outcome of days without organ support in the critically ...
https://www.massgeneral.org › news › coronavirus PDF
Hematology Recommendations and Dosing Guidelines during ...
Dec 12, 2020 — Hematology Recommendations and Dosing Guidelines during COVID-19 ... Patients who need to be on Unfractionated Heparin (instead of LMWH).
https://www.hematology.org › covid-19 › covid-19-an...
COVID-19 and VTE-Anticoagulation - Hematology.org
The risk of VTE following hospital discharge appears low based on ... discourage the empiric use of full dose heparin or LMWH in this subgroup of COVID-19 ...

Potential AHRQ Knowledge Portal (Concept Demo)

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FEvIR Platform

COVID Anticoagulation

Limit to after YYYY-MM-DD and before YYYY-MM-DD

- Guidance ▼
  - Clinical Decision Support ►
  - Guidelines ▼
    - Organized Collections of Guidelines
    - Lists of Guidelines
    - Single Guidelines 4
  - Recommendations ▼
    - Organized Collections of Recommendations 1
    - Lists of Recommendations
    - Single Recommendations 10
- Evidence ▼
  - Organized Collections of Systematic Reviews
  - Lists of Systematic Reviews
  - Single Systematic Reviews 4
  - Organized Collections of Studies 1
  - Lists of Studies 1
  - Single Studies 5
  - Planned Studies 5
- Quality Improvement & Innovation ►
- Healthcare Costs and Access
- Resource Collections & Toolkits

AHRQ Knowledge Portal (Demo)

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List View | Detail View | About Portal | X

Guidance

Guidelines

Single Guidelines 4

- Australian guidelines for the clinical care of people with COVID-19 (2021-09-28)
- ASH Guidelines on Use of Anticoagulation in Patients with COVID-19 (2021-09-02)
- COVID-19 Clinical Management (2021-01-25T17:00:00.000Z)
- NIH COVID-19 Treatment Guidelines: Antithrombotic Therapy in Patients with COVID-19 (2021-02-11)

Recommendations

Organized Collections of Recommendations 1

- Anticoagulation for COVID-19 - Recommendations Summary Browser Demo from ACTS COVID-19 Collaborative (2021-09-10)

Single Recommendations 10

- ASH Recommendation 1a - anticoagulation for critically ill patients with COVID-19 (2021-04-07)
- WHO recommendation on prophylactic anticoagulation in hospitalized patients with COVID-19 - same for critical care (2021-01-25)
- WHO recommendation on prophylactic anticoagulation in hospitalized patients with COVID-19 (2021-01-25)
- NIH anticoagulant recommendation for nonhospitalized COVID-19 (2021-02-11)
- NIH anticoagulant recommendation for hospitalized nonpregnant COVID-19 in critical care (2021-02-11)
- NIH anticoagulant recommendation for hospitalized nonpregnant COVID-19 (2021-02-11)
- ASH Recommendation 2 - anticoagulation for non-critically ill inpatients with COVID-19 (2020-11-02)
- Australian recommendation on VTE prophylaxis for adults (from website) (2021-07-14)
- Australian recommendation on VTE prophylaxis for adults (from MAGICapp) (2021-09-28)
- ASH DRAFT Recommendation 3 - anticoagulation for discharged hospitalized patients with COVID-19 (2021-07-08)

Evidence

Single Systematic Reviews 4

- Effect of Anticoagulant Administration on the Mortality of Hospitalized Patients With COVID-19: An Updated Systematic Review and Meta-Analysis. (2021)
- A Systematic Review and a Meta-Analysis Comparing Prophylactic and Therapeutic Low Molecular Weight Heparins for Mortality Reduction in 32,688 COVID-19 Patients. (2021)
- Anticoagulation for Non-critically ill COVID-19 Summary of Findings from RCTs Table EvidenceReport (2021-09-09)
- Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. (2021-09-14)

Organized Collections of Studies 1

- Anticoagulation for Non-critically ill COVID-19 Individual RCTs Table EvidenceReport (2021-09-03)

Lists of Studies 1

https://fevir.net/knowledgeportaldemo

Recommendations Summary Browser

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Computable Publishing: Recommendations Table Viewer

(Anticoagulation for COVID-19 - Recommendations Summary Browser Demo from ACTS COVID-19 Collaborative)

For COVID Patients In:	Critical Care	Hospitalized (not critical)	Outpatient
ASH Recommends:	Suggests using prophylactic-intensity anticoagulation Strength: conditional recommendation Last review date: 2021-04-07	Prophylactic-intensity over DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at intermediate-intensity or therapeutic-intensity Strength: weak Last review date: 2020-10-26	Suggests NOT using anticoagulant outpatient thromboprophylaxis after hospital discharge Strength: conditional recommendation - DRAFT RECOMMENDATION Last review date: 2021-07-08
NIH Recommends:	Provide prophylactic dose anticoagulation Strength: AIII Last review date: 2021-02-11	Provide prophylactic dose anticoagulation Strength: AIII Last review date: 2021-02-11	Do NOT initiate prophylactic anticoagulation or antiplatelet therapy Strength: AIII Last review date: 2021-02-11
WHO Recommends:	Anticoagulation at prophylactic intensity Strength: weak Last review date: 2021-01-25	Anticoagulation at prophylactic intensity Strength: weak Last review date: 2021-01-25	
Australian Guidelines Recommends:	Use prophylactic doses of anticoagulants, preferably low molecular weight heparin (LMWH) Strength: Conditional recommendation Last review date: 2021-07-14	Do not routinely offer therapeutic anticoagulant dosing Strength: weak	

Please contribute to the discussion: Should recently published evidence or guidance on anticoagulation for COVID-19 change clinical practice?

The COVID-19 Knowledge Accelerator is coordinating efforts for many to contribute to post-publication review of evidence comparing therapeutic-dose anticoagulation and prophylactic-dose anticoagulation in non-critically ill patients hospitalized for COVID-19. Let's show how many citizens, scientists, information specialists, and stakeholders can contribute to multidisciplinary post-publication review and improvement of scientific communication. Current summaries of the evidence include the primary outcome of the NEJM Aug 4 multi-platform RCT (https://fevir.net/7637), the transformed primary outcome of the NEJM Aug 4 multi-platform RCT (https://fevir.net/7639), the primary composite outcome of the RAPID trial Preprint (https://fevir.net/18098), and a secondary outcome (all-cause mortality) from the RAPID trial Preprint (https://fevir.net/18136). You can put any of those links into your browser to see the current evidence summaries developed from this coordinated effort.

Search for Systematic Reviews about "Antithrombotic agents for COVID-19" in LOVE Platform (latest entry added: 2021-07-14)

Search for RCTs about "Antithrombotic agents for COVID-19" in LOVE Platform (latest entry added: 2021-07-14)

Search for High Quality Evidence on Prophylactic Anticoagulation in COVID-19 Evidence Alerts from McMaster PLUS™ (latest entry added: 2021-08-27)

Recommendation Viewer

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WHO recommendation on prophylactic anticoagulation in hospitalized patients with COVID-19

Navigation

- Summary
- Population
- Action
- Implementation
- Evidence
- Justification
- Classifiers
- Metadata

Communicate

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Text View | JSON View | Usage View

X

Summary

Title: WHO recommendation on prophylactic anticoagulation in hospitalized patients with COVID-19

Description: The World Health Organization (WHO) recommends, in hospitalized patients with COVID-19, without an established indication for higher dose anticoagulation, we suggest administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing.

Recommending Organization: World Health Organization (WHO)

For the Population: COVID-19 - Hospitalized (not critical)

Recommended Action: Anticoagulation at prophylactic intensity

Strength of Recommendation: weak

Guideline Reference:
URL: https://fevir.net/resources/Citation/2879
Citation Resource: Citation/2879

Cite As: WHO recommendation on prophylactic anticoagulation in hospitalized patients with COVID-19 [FHIR Resource]. In: Fast Evidence Interoperability Resources (FEvIR) Platform. Revised January 25, 2021. Available at: https://fevir.net/resources/Recommendation/2880. Computable resource at: https://fevir.net/resources/Recommendation/2880. (Citation/27258)

Population

Adults hospitalized with COVID-19 without indication for therapeutic anticoagulation

Inclusion Criteria

Type of Characteristic	Characteristic Value
Admission to establishment (procedure)	Hospital admission
Age	>= 18 year
Disease (disorder)	COVID-19 confirmed

Exclusion Criteria

Type of Characteristic	Characteristic Value
Disease (disorder)	Thromboembolic disorder

Resource Reference
Adults hospitalized with COVID-19 without indication for therapeutic anticoagulation

Recommendation Viewer

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WHO recommendation on prophylactic anticoagulation in hospitalized patients with COVID-19

Navigation

- Summary
- Population
- Action
- Implementation
- Evidence
- Justification
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TY | Share | Comment | Ask

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Evidence

Evidence Certainty:

Type	Rating	Rater	Description	Notes
Overall certainty	Very low quality			

Evidence Detail:

mortality outcome for WHO COVID anticoag recommendation
Evidence Resource

Pulmonary embolism outcome for WHO COVID anticoag recommendation
Evidence Resource

Major bleeding outcome for WHO COVID anticoag recommendation
Evidence Resource

loveLink
URL

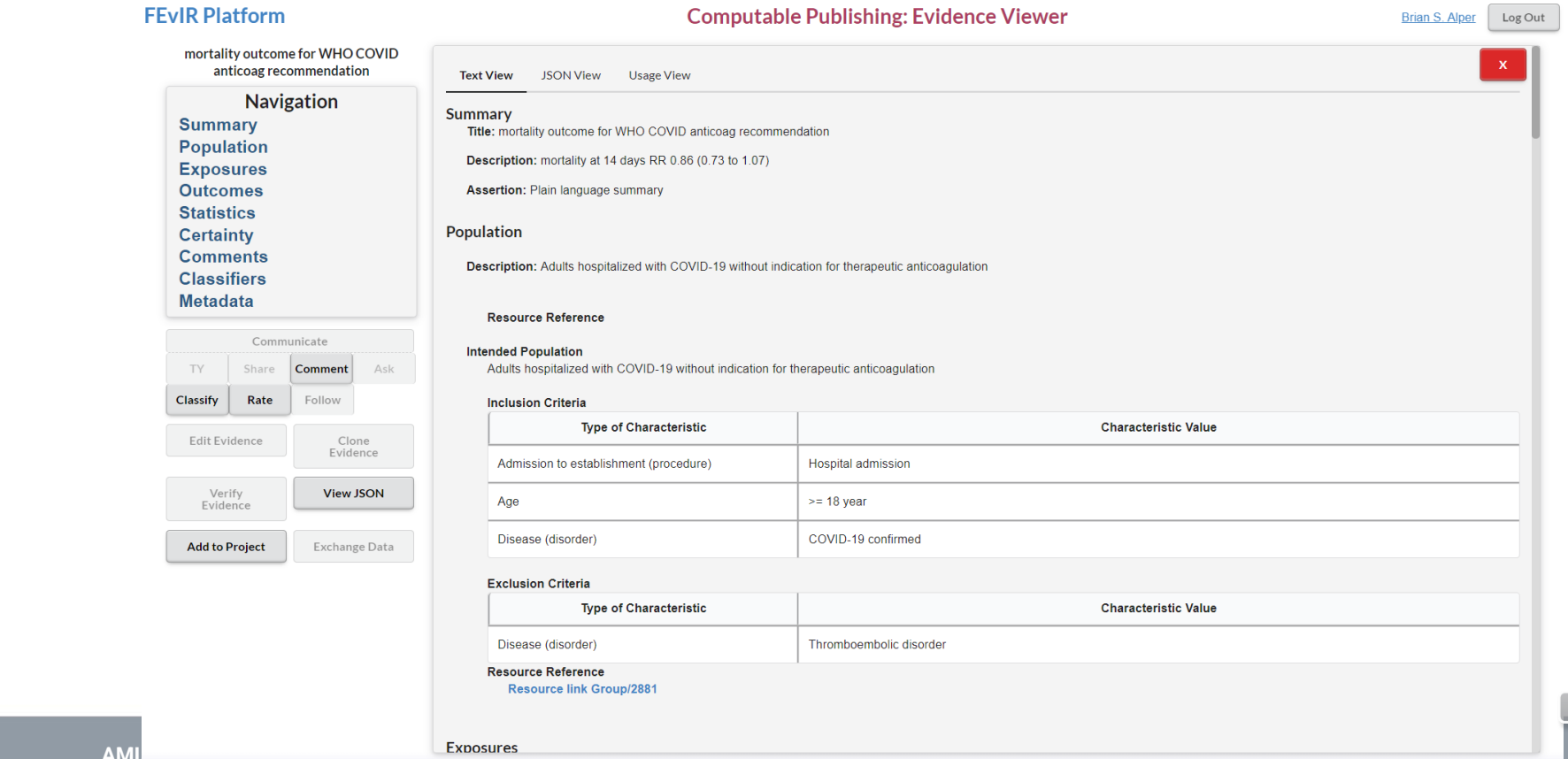
Justification

Summary: When moving from evidence to the conditional recommendation in favour of standard thromboprophylaxis anticoagulation for patients with moderate, severe, and critical COVID-19, the panel emphasized the very low certainty evidence of reduction in mortality or pulmonary embolism with higher anticoagulant dosing. The panel recognized that the evidence supporting an increased risk of major bleeding was dominated by studies of therapeutic anticoagulation rather than intermediate dosing. The Guideline Development Group (GDG) panellists anticipated variability in patient values and preferences, and judged that other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation. The panel acknowledged that ongoing randomized trials are expected to add substantially to the evidence base over the next several months.

Net Benefit:

Preferences:

Evidence Viewer



Evidence Viewer

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mortality outcome for WHO COVID anticoag recommendation

Navigation

- Summary
- Population
- Exposures
- Outcomes
- Statistics
- Certainty
- Comments
- Classifiers
- Metadata

Communicate

TY | Share | Comment | Ask

Classify | Rate | Follow

Edit Evidence | Clone Evidence

Verify Evidence | View JSON

Add to Project | Exchange Data

Statistics

Statistic #1

Description: RR 0.86

Relative Risk	**0.86**

Sample Size:

1 studies, 5252 participants

Attribute	Value	Notes
95% Confidence interval	0.73 to 1.07	**Description:** 95% CI 0.73 to 1.07

Statistic #2

Description: risk difference (95% CI) from 38 fewer per 1000 to 3 more per 1000

Risk Difference	

Sample Size:

1 studies, 5252 participants

Attribute	Value	Notes
95% Confidence interval	-0.038 to 0.003	

Certainty

Type	Rating	Description	Notes	Rater
Overall certainty	Very low quality	Very low certainty	Due to very serious risk of bias. Due to very serious imprecision.	
Risk of bias	very serious concern	very serious risk of bias		
Imprecision	very serious concern	very serious imprecision		

Comments

But new evidence was published

RESEARCH SUMMARY

Therapeutic Anticoagulation with Heparin in Critically Ill and Noncritically Ill Patients with Covid-19

DOI: 10.1056/NEJMoa2103417 and DOI: 10.1056/NEJMoa2105911

CLINICAL PROBLEM

Thrombosis and inflammation may contribute to the risk of death and complications among patients with Covid-19. The safety and effectiveness of therapeutic doses of heparin to improve clinical outcomes are not known.

CLINICAL TRIAL

Design: A multiplatform, open-label, adaptive, randomized, controlled trial evaluated anticoagulation strategies in patients hospitalized with Covid-19.

Intervention: 2219 patients with moderate Covid-19 and 1098 with severe Covid-19 requiring ICU-level care were randomly assigned to receive therapeutic-dose anticoagulation (unfractionated or low-molecular-weight heparin) or usual-care pharmacologic thromboprophylaxis. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death and the number of days free of organ support up to day 21.

RESULTS

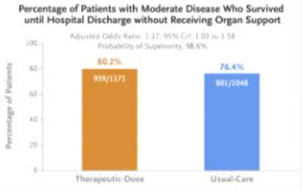
Efficacy: Among patients with moderate disease, those given therapeutic-dose anticoagulation had a higher probability of survival without cardiovascular or respiratory support than those given usual care. In patients with severe Covid-19, therapeutic anticoagulation was inferior to usual-care thromboprophylaxis. In the cohort with moderate Covid-19, the criterion for superiority was met, and in the critically ill cohort, the criterion for futility was met.

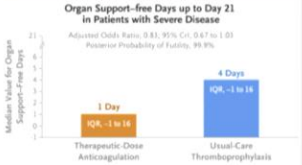
Safety: Rates of major bleeding were low and were driven mostly by the need for red cell transfusion.

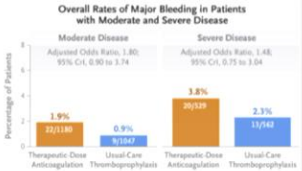
LIMITATIONS

- The majority of the critically ill patients were enrolled in the United Kingdom, where guidelines changed during the trial, and thus many patients in the usual-care group received intermediate-dose thromboprophylaxis.
- Detailed participant screening data were not available, so common reasons for exclusion from the trials are unknown, potentially limiting generalizability.

Links: Full Article (The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med 2021;385:777-89.) | **Full Article** (The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 2021;385:790-802.) | **NEJM Quick Take** | **Editorial**







CONCLUSIONS

Therapeutic doses of heparin, as compared with usual-care venous thromboprophylaxis, increased the probability of surviving to hospital discharge with fewer days of cardiovascular or respiratory support in patients with moderate Covid-19 but not in those with severe Covid-19.

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Heparin for Moderately Ill Patients with Covid-19

Michelle Sholzberg, Grace H. Tang, Hassan Rahhal, Musaad AlHamzah, Lisa Baumann Kreuziger, Fionnuala Ní Áinle, Faris Alomran, Khalid Alayed, Mohammed Alsheef, Fahad AlSumait, Carlos Eduardo Pompilio, Catherine Sperlich, Sabrena Tangri, Terence Tang, Peter Jaksa, Deepa Suryanarayan, Mozah Almarshoodi, Lana Castellucci, Paula D. James, David Lillicrap, Marc Carrier, Andrew Beckett, Christos Colovos, Jai Jayakar, Marie-Pier Arsenault, Cynthia Wu, Karine Doyon, E. Roseann Andreou, Vera Dounaevskaia, Eric K. Tseng, Gloria Lim, Michael Fralick, Saskia Middeldorp, Agnes Y.Y. Lee, Fei Zuo, Bruno R. da Costa, Kevin E. Thorpe, Elnara Márcia Negri, Mary Cushman, Peter Jüni, the RAPID Trial investigators

doi: https://doi.org/10.1101/2021.07.08.21259351

Now accepted for publication in *BMJ*

Abstract | Full Text | Info/History | Metrics | Preview PDF

Abstract

Background Heparin, in addition to its anticoagulant properties, has anti-inflammatory and potential anti-viral effects, and may improve endothelial function in patients with Covid-19. Early initiation of therapeutic heparin could decrease the thrombo-inflammatory process, and reduce the risk of critical illness or death.

Methods We randomly assigned moderately ill hospitalized ward patients admitted for Covid-19 with elevated D-dimer level to therapeutic or prophylactic heparin. The primary outcome was a composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission. Safety outcomes included major bleeding. Analysis was by intention-to-treat.

Results At 28 days, the primary composite outcome occurred in 37 of 228 patients (16.2%) assigned to therapeutic heparin, and 52 of 237 patients (21.9%) assigned to prophylactic heparin (odds ratio, 0.69; 95% confidence interval [CI], 0.43 to 1.10; p=0.12). Four patients (1.8%) assigned to therapeutic heparin died compared with 18

Posted July 12, 2021.

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COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv

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Hematology

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- ☐ Guidance ▼
  - ☐ Clinical Decision Support ►
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    - ☐ Organized Collections of Guidelines
    - ☐ Lists of Guidelines
    - ☐ Single Guidelines 4
  - ☐ Recommendations ▼
    - ☐ Organized Collections of Recommendations 1
    - ☐ Lists of Recommendations
    - ☐ Single Recommendations 10
- ☑ Evidence ▼
  - ☐ Organized Collections of Systematic Reviews
  - ☐ Lists of Systematic Reviews
  - ☑ Single Systematic Reviews 4
  - ☑ Organized Collections of Studies 1
  - ☑ Lists of Studies 1
  - ☑ Single Studies 6
  - ☑ Planned Studies 6
- ☐ Quality Improvement & Innovation ►
- ☐ Healthcare Costs and Access
- ☐ Resource Collections & Toolkits

AHRQ Knowledge Portal (Demo)

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List View | Detail View | About Portal | X

Evidence

Single Systematic Reviews 4

- Effect of Anticoagulant Administration on the Mortality of Hospitalized Patients With COVID-19: An Updated Systematic Review and Meta-Analysis. (2021)
- A Systematic Review and a Meta-Analysis Comparing Prophylactic and Therapeutic Low Molecular Weight Heparins for Mortality Reduction in 32,688 COVID-19 Patients. (2021)
- Anticoagulation for Non-critically ill COVID-19 Summary of Findings from RCTs Table EvidenceReport (2021-09-09)
- Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. (2021-09-14)

Organized Collections of Studies 1

- Anticoagulation for Non-critically ill COVID-19 Individual RCTs Table EvidenceReport (2021-09-03)

Lists of Studies 1

- ClinicalTrials.gov search for COVID Anticoagulation (2021-10-07T18:40:04.666Z)

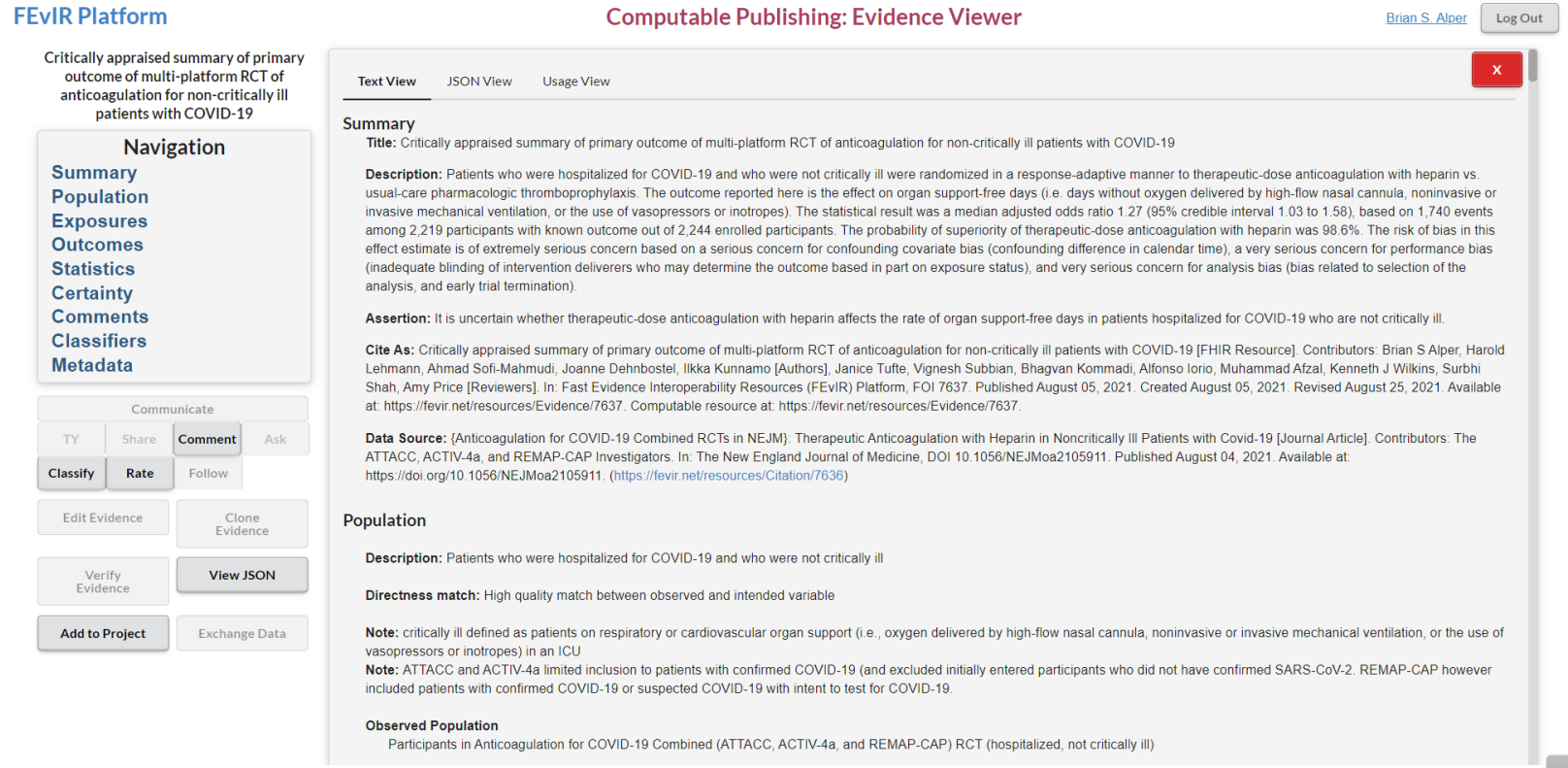
Single Studies 6

- Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. (2021-10-07)
- Anticoagulant Therapy in Patients Hospitalized With COVID-19. (2021-10-07)
- Anticoagulation for Non-critically ill COVID-19 Multiplatform RCT EvidenceReport (2021-09-02)
- Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19 (2021-08-04)
- Anticoagulation for Non-critically ill COVID-19 RAPID trial RCT EvidenceReport (2021-09-02)
- Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. (2021-04-27)

Planned Studies 6

- CT.gov entry: Full Dose Heparin Vs. Prophylactic Or Intermediate Dose Heparin in High Risk COVID-19 Patients (2021-08-05)
- CT.gov entry: Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (2020-10-12)
- CT.gov entry: Anti-thrombotics for Adults Hospitalized With COVID-19 (ACTIV-4) (2021-03-20)
- CT.gov entry: A Randomized Trial of Anticoagulation Strategies in COVID-19 (2020-10-08)
- CT.gov entry: Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) (2021-07-27)
- CT.gov entry: Intermediate-dose vs Standard Prophylactic Anticoagulation and Statin vs Placebo in ICU Patients With COVID-19 (2021-08-17)

Evidence Viewer



Evidence Viewer

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Critically appraised summary of primary outcome of multi-platform RCT of anticoagulation for non-critically ill patients with COVID-19

Navigation

- Summary
- Population
- Exposures
- Outcomes
- Statistics
- Certainty
- Comments
- Classifiers
- Metadata

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Population

Description: Patients who were hospitalized for

Directness match: High quality match between

Note: critically ill defined as patients on respirato
vasopressors or inotropes) in an ICU
Note: ATTACC and ACTIV-4a limited inclusion to
included patients with confirmed COVID-19 or su

Observed Population

Participants in Anticoagulation for COVID-19

Inclusion Criteria

Type of Characteristic
Research Study for which this is the observ
Admission to establishment (procedure)
Disease (disorder)

Exclusion Criteria

Type of Characteristic	Characteristic Value
Severity	Life threatening severity, severe disease defined as ICU-level care or critically ill where ICU-level care was defined as the use of respiratory or cardiovascular organ support (oxygen delivered by high-flow nasal cannula, noninvasive or invasive mechanical ventilation, or the use of vasopressors or inotropes)

Resource Reference

Participants in Anticoagulation for COVID-19 Combined (ATTACC, ACTIV-4a, and REMAP-CAP) RCT
Resource link Group/7750

Intended Population

Patients who are hospitalized for COVID-19 and who are not critically ill

Intended Population

Patients who are hospitalized for COVID-19 and who are not critically ill

Inclusion Criteria

Type of Characteristic	Characteristic Value
Admission to establishment (procedure)	Hospital admission
Disease (disorder)	Disease caused by severe acute respiratory syndrome coronavirus 2 (disorder)

Exclusion Criteria

Type of Characteristic	Characteristic Value
Severity	Life threatening severity

Resource Reference

Patients who are hospitalized for COVID-19 and who are not critically ill
Resource link Group/7749

support@computablepublishing.com

Evidence Viewer

FEvIR Platform

Computable Publishing: Evidence Viewer

Brian S. Alper | Log Out

Critically appraised summary of primary outcome of multi-platform RCT of anticoagulation for non-critically ill patients with COVID-19

Navigation

- Summary
- Population
- Exposures
- Outcomes
- Statistics
- Certainty
- Comments
- Classifiers
- Metadata

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Edit Evidence | Clone Evidence

Verify Evidence | View JSON

Add to Project | Exchange Data

Statistics

Description: median adjusted odds ratio 1.27 (95% credible interval 1.03 to 1.58)
Note: 939 out of 1171 (80.2%) in therapeutic-dose anticoagulation group
Note: 801 out of 1048 (76.4%) in usual-care thromboprophylaxis group

Odds Ratio	1.27

Number of Events: 1740
Sample Size:
3 studies, 2244 participants, 2219 counted
Note: 19 (1.6%) therapeutic-dose group and 6 (0.6%) usual-care group were excluded from primary analysis

Attribute	Value	Notes
95% Credible interval	1.03 to 1.58	
probability of superiority	0.986	

Model Characteristics	Details
Hierarchical Bayesian Cumulative Logistic Regression with Dynamic Borrowing	
weakly informative Dirichlet prior distributions for the number of days without organ support	
The model was fitted with the use of a Markov chain Monte Carlo algorithm with 100,000 samples from the joint posterior distribution, which allowed for calculation of the posterior distributions for the proportional odds ratios, including medians and 95% credible intervals, and the posterior probabilities of superiority and futility for the comparison between therapeutic-dose anticoagulation and usual-care thromboprophylaxis.	
median value used for reporting the effect estimate	
Adjusted analysis Adjustment variables include age, sex, trial site, d-dimer cohort, and enrollment period (in 2-week intervals).	Adjusted for: • age (continuous) • sex (dichotomous) • trial site (categorical) • d-dimer cohort (categorical) • enrollment period (ordinal)

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Certainty

Type				
Risk of bias				
Selection Bias				
Confounding Covariate Bias				
Allocation Bias	Adaptive randomization is not a concern by itself, only if it results in a confounding difference.	Response-adaptive randomization led to imbalanced randomization.	Definition of Allocation Bias = A confounding covariate bias resulting from methods for assignment of the independent variable by the investigator to evaluate a response or outcome. ATTACC implemented response-adaptive randomization on December 15, 2020, which led to imbalanced randomization.	Brian S. Alper, Joanne Dehnbostel, Harold Lehmann, Kenneth Wilkins
Confounding difference	serious concern	There is an unequal distribution of calendar time between the groups being compared.	Definition of Confounding difference = A confounding covariate bias in which the unequal distribution of a potentially distorting variable is recognized. Incomplete reporting limits the determination of the potential degree of influence of calendar time. There is evidence of potential for calendar time to influence the results: In an observational study of 18,508 adults with laboratory-confirmed, COVID-19 associated hospitalization 'The percentage of hospitalized patients admitted to the ICU decreased from 37.8% in March to 20.5% in December' (Ann Intern Med 2021 Aug 10 https://www.acpjournals.org/doi/10.7326/M21-1991).	Brian S. Alper, Joanne Dehnbostel, Harold Lehmann, Kenneth Wilkins
Performance Bias	very serious concern	Awareness of treatment assignment may reduce clinical decision to initiate some types of "organ support" in patients with higher risk of major bleeding.	Definition of Performance Bias = A bias resulting from differences between the received exposure and the intended exposure.	Brian S. Alper, Joanne Dehnbostel, Harold Lehmann, Muhammad Afzal
Inadequate blinding of intervention deliverers	very serious concern	Lack of blinding may explain reported differences in the primary outcome.	The absolute difference in survival without intubation was 1%, so 3% of the 4% absolute difference in the primary outcome can be considered "organ support without intubation"	Brian S. Alper; clarifying explanation reviewed by Janice Tufte
			for this concern and the appropriateness of any sensitivity analyses.	

EvidenceReport Viewer

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Anticoagulation for Non-critically ill COVID-19 Summary of Findings from RCTs Table EvidenceReport

Navigation

- Summary
- Table View
- Populations
- Exposures
- Results
- Risk of Bias
- Metadata

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Add to Project | Exchange Data

Table View

Outcome	Sample size (# trials, # participants, # counted, # events)	Result with prophylactic anticoagulation	Result with therapeutic anticoagulation	Effect estimate (therapeutic dose effect)	Certainty of finding (Quality of evidence)	What this means
Organ support-free days alive at 21 days (EvidenceVariable/7753)	2 trials, 2684 participants (Evidence/18868)	Not reported	Not reported	odds ratio 1.31 (95% confidence interval 1.08 to 1.60) (Evidence/18868)	Very low certainty due to risk of bias, inconsistency, and imprecision (Evidence/18868)	It is uncertain whether therapeutic-dose anticoagulation with heparin affects the likelihood of organ support-free days alive at 21 days in patients hospitalized for COVID-19 who are not critically ill. (Evidence/18868)
Mortality at 28 days (EvidenceVariable/230)	2 trials, 2,684 participants, 2,684 counted,194 events (Evidence/18812)	81 out of 1,000 (8.1%)	61 out of 1,000 (6.1%) 95% CI 45 to 82 out of 1,000 (4.5% to 8.2%) (Evidence/18812)	Risk difference -2% (95% CI -3.6% to 0.1%) 20 fewer out of 1,000 (95% CI 36 fewer to 1 more) (Evidence/18812)	Very low certainty due to risk of bias, inconsistency, and imprecision (Evidence/18812)	It is uncertain whether therapeutic-dose anticoagulation with heparin affects the likelihood of any death at 28 days in patients hospitalized for COVID-19 who are not critically ill. (Evidence/18812)
Survival without organ support at 21 days (EvidenceVariable/7754)	1 trial*, 2,244 participants, 2,219 counted, 1,740 events (Evidence/7639)	764 out of 1,000 (76.4%) (Evidence/18814)	804 out of 1,000 (80.4%) 95% credible interval 769 to 836 out of 1,000 (76.9% to 83.6%) (Evidence/7639, Evidence/18814, Evidence/18813)	Risk difference 4% (95% credible interval 0.5% to 7.2%) 40 more out of 1,000 (95% credible interval 5 more to 72 more) (Evidence/7639)	Very low certainty due to risk of bias (Evidence/7639)	It is uncertain whether therapeutic-dose anticoagulation with heparin affects the likelihood of any death or organ support in patients hospitalized for COVID-19 who are not critically ill. (Evidence/7639)
Death or ICU admission by 28 days (EvidenceVariable/18134)	1 trial, 465 participants, 465 counted, 89 events (Evidence/18098)	219 out of 1,000 (21.9%) (Evidence/18098)	162 out of 1,000 (16.2%) 95% CI 105 to 236 out of 1,000 (10.5% to 23.6%) (Evidence/18098)	Risk difference -5.7% (95% CI -11.4% to 1.7%) 57 fewer out of 1,000 (95% CI 114 fewer to 17 more) (Evidence/18098)	Low certainty due to risk of bias and imprecision (Evidence/18098)	It is uncertain whether therapeutic-dose anticoagulation with heparin affects the rate of death or critical care in patients hospitalized for COVID-19 who are not critically ill. (Evidence/18098)

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Helping the Helpers on the Patient Journey

We may not expect Mae to directly view this computable evidence and guidance when she is lying in the hospital bed, but...

- The computable recommendations are immediately available for the clinician seeking the guidance, and...
- The computable evidence (technically also immediately available) has been used by guideline developers and CDS developers questioning these decisions now while the guidelines have not yet incorporated this new evidence.

How do we do this on scale?

1. Agree to a common standard for data exchange – EBMonFHIR
2. Map your current systems and tools to read from and/or write to FHIR
3. Agree to common terminologies (code systems) for data exchange
4. Map your current systems and tools to read from and/or write to common code systems
5. Use the systems and tools to make your job easier (whatever job you have related to evidence and guidance)
6. Give feedback to system and tool developers to make the tools better.

COKA How to Participate

For all of these meetings: Join Microsoft Teams Meeting

If you wish to learn more about COKA please go to Tinyurl.com/coka2020

Questions: balper@computablepublishing.com

COKA COVID-19 Knowledge Accelerator

Day	Time (Eastern)	Team
Monday	8-9 am	Project Management
Monday	9-10 am	Systematic Meta-Review Project Group
Monday	11am-12pm	Computable EBM Tools Development Working Group
Monday	1-2 pm	Terminology and Ontology WG
Tuesday	10-11 am	Recommendation Profile WG
Tuesday	11am-12pm	Common Metadata Framework WG
Tuesday	2-3 pm	Research Design WG
Wednesday	8-9 am	Knowledge Ecosystem Liaison WG
Wednesday	9-10 am	Statistic Standard and Terminology WG
Thursday	9-10 am	Computable EBM Tools Development Working Group
Thursday	4-5 pm	Project Management
Friday	9-10 am	Risk of Bias Terminology and Tooling WG
Friday	10-11 am	Communications (Awareness, Scholarly Publications) WG

Thank you!

Email me at:
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