Evidence Brief: Anticoagulation for Hospitalized Adults with COVID-19

Supplemental Materials

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APPENDIX A: SEARCH STRATEGY

DATABASE: OVID MEDLINE

1. Middle East Respiratory Syndrome Coronavirus/ or SARS Virus/
2. (Severe Acute Respiratory Syndrome Coronavirus 2 or COVID-19 or COVID19 or novel coronavirus or coronavirus or corona virus or SARS-CoV or SARS-CoV-2 or SARS2 or 2019-nCoV or Middle East Respiratory Syndrome or MERS or MERS virus or MERS viruses or MERS-CoV or Severe Acute Respiratory Syndrome or SARS or SARS-CoV or SARS coronavirus).ti,ab,kf.
3. 1 or 2
4. Thrombophilia/ or Blood Coagulation/ or exp Thrombosis/ or exp Anticoagulants/
5. (thrombosis or thrombotic or blood clot$1 or coagulation or hypercoagulative or embolic or embolus or anticoagulant$1).ti,ab,kf.
6. 4 or 5
7. 3 and 6
8. Limit 7 to yr="2003-Current"

DATABASE: WHO COVID-19 LITERATURE DATABASE

1. (tw:(thrombosis OR thrombotic OR blood clot OR blood clots OR coagulation OR coagulative OR coagulate OR hypercoagulation OR hypercoagulative OR hypercoagulate OR anticoagulation OR anticoagulate OR anticoagulative OR embolic OR embolus))

APPENDIX B: EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible setting, 6=Ineligible study design (*ie*, case report, etc.) 7=Ineligible publication type (*ie*, narrative review, commentary, pre-print, *etc*), 8=Outdated or ineligible systematic review, 9=Non-English language.

Citation	Exclude reason
Pro-thrombotic Status in Patients with SARS-CoV-2 Infection (ATTAC-Co). ClinicalTrials.gov Identifier: NCT04343053 https://clinicaltrials.gov/ct2/show/NCT04343053?term=Pro-thrombotic+Status+in+Patients+with+SARS-CoV-2+Infection+%28ATTAC-Co%29&draw=2&rank=1. Updated April 13. Accessed April 24, 2020.	E2
Dociparstat for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure: ClinicalTrials.gov Identifier: NCT04389840. https://clinicaltrials.gov/ct2/show/NCT04389840?cond=covid19&sfpd_s=04%2F20%2F2020&sfpd_e=05%2F15%2F2020&sort=nwst&draw=2&rank=22. Updated May 15, 2020. Accessed June 2, 2020.	E7
Preventing Cardiac Complication of COVID-19 Disease With Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial. (C-19-ACS). ClinicalTrials.gov Identifier: NCT04333407. Imperial College London. https://clinicaltrials.gov/ct2/show/NCT04333407?term=NCT04333407&draw=2&rank=1. Published 2020. Updated April 9, 2020. Accessed April 13, 2020.	E7
COVID-19 and Deep Venous Thrombosis. ClinicalTrials.gov Identifier: NCT04338932. https://clinicaltrials.gov/ct2/show/NCT04338932?term=NCT04338932&draw=2&rank=1. Published 2020. Updated April 8, 2020. Accessed April 13, 2020.	E6
Preventing COVID-19 Complications With Low- and High-dose Anticoagulation (COVID-HEP). ClinicalTrials.gov Identifier: NCT04345848. https://clinicaltrials.gov/ct2/show/NCT04345848?term=NCT04345848&draw=2&rank=1. Published 2020. Updated April 15, 2020. Accessed April 24, 2020.	E7
Austrian CoronaVirus Adaptive Clinical Trial (ACOVACT). ClinicalTrials.gov Identifier: NCT04351724. https://clinicaltrials.gov/ct2/show/NCT04351724?term=Austrian+CoronaVirus+Adaptive+Clinical+Trial+%28ACOVACT%29&draw=2&rank=1. Published 2020. Updated April 24, 2020. Accessed April 24, 2020.	E7
Trial Evaluating Efficacy and Safety of Anticoagulation in Patients With COVID-19 Infection, Nested in the Corimmuno-19 Cohort (CORIMMUNO-COAG). ClinicalTrials.gov Identifier: NCT04344756. https://clinicaltrials.gov/ct2/show/NCT04344756?term=NCT04344756&draw=2&rank=1. Published 2020. Updated April 15, 2020. Accessed April 24, 2020, 2020.	E6
Analysis of the Coagulopathy Developed by COVID-19 Infected Patients: Thrombin Generation Potential in COVID-19 Infected Patients. ClinicalTrials.gov Identifier: NCT04356950 https://clinicaltrials.gov/ct2/show/NCT04356950?term=Analysis+of+the+Coagulopathy+Developed+by+COVID-19+Infected+Patients%3A+Thrombin+Generation+Potential+in+COVID-19+Infected+Patients&draw=2&rank=1. Published 2020. Updated April 22. Accessed April 24, 2020.	E7
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Pathogenesis of COVID-19. Role of heparins in the therapy of severe conditions in patients with COVID-19. Akusherstvo i Ginekologiya (Russian Federation). 2020;2020(12).	E7
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APPENDIX C: EVIDENCE TABLES

Note: The below tables summarize reported effect information; analytic data, included for studies whose effect sizes were calculated after data abstraction, are available upon request.

OUTCOME DATA OF INCLUDED PRIMARY STUDIES

Mortality in Hospitalized COVID-19 Patients Receiving Intermediate-dose Anticoagulation Compared to Standard Thromboprophylaxis

Author Year	Study Type	N	Baseline Severity	Length of Observation Period (days)	Adjustment	Results
Hazard Ratios						
Bikdeli[1]	RCT	562	Severe or critical	90	Treatment site	HR=1.24 (95%CI [0.97-1.60])
Perepu[2]	RCT	176	Severe or critical	30	None (randomized)	HR=0.57 (95%CI [0.28-1.17])
Jonmarker[3]	Cohort	152	Severe or critical	28	Baseline severity and covariates	HR=0.88 (95%CI [0.43-1.83])
Martinelli[4]	Cohort	278	Mixed	21	Covariates	HR=0.36 (95%CI [0.18-0.76])
Meizlish[5]	Cohort	382	Mixed	NR	Baseline severity and covariates	HR=0.518 (95%CI [0.308-0.872])
Tacquard[6]	Cohort	538	Severe or critical	14	None	HR=1.12 (95%CI [0.78-1.62])
Risk Ratios						
Hsu[7]	Cohort	441	Mixed	30	Baseline severity and covariates	RR=0.26 (95%CI [0.07-0.97])%
Odds Ratios						
Jiménez-Soto[8]	Cohort	321	Mixed	NR	Baseline severity and covariates	OR=0.30 (95%CI [0.08-1.16])
Kumar[9]	Cohort	4645	Mixed	NR	Baseline severity and covariates	OR=1.62 (95%CI [0.65-4.05])
Lavinio[10]	Cohort	852	Severe or critical	13*	Baseline severity and covariates	Log odds=0.663 (95%CI [0.16-1.17])**
Paolisso[11]	Cohort	450	Mixed	10*	Baseline severity and covariates	OR=0.26 (95%CI [0.089-0.758])
Stessel[12]	Cohort	72	Severe or critical	30	Baseline severity and covariates	OR=8.86 (95%CI [1.46-53.75])$
Proportion Comparison (intermediate-dose anticoagulation vs standard-dose thromboprophylaxis, p-value if reported)						
Arachchillage[13]	Cohort	171	Mixed	NR	None	12/110 (11%) vs 13/61 (21%)
Gabara[14]	Cohort	201	Severe or critical	100	None	17/94 (18%) vs 17/78 (22%)

Author Year	Study Type	N	Baseline Severity	Length of Observation Period (days)	Adjustment	Results
Moll[15]	Cohort	94	Severe or critical	28	Baseline severity and covariates	12/47 (26%) vs 13/47 (28%)
Pesavento[16]	Cohort	324	Moderate	30	Covariates	14/84 (17%) vs 27/240 (11%)
Voicu[17]	Cohort	93	Severe or critical	NR	None	20/43 (47%) vs 18/50 (36%)

Notes.
*Median observation length
** Analysis reports unscaled log odds instead of odds ratio; a value >0 (including <1) indicates survival benefit of intermediate prophylaxis.
$ Odds ratio >1 indicates improved mortality with intermediate-dose prophylaxis.
% Analytical sample is n=265 participants with no explanation for exclusions

Mortality in Hospitalized COVID-19 Patients Receiving Therapeutic Anticoagulation Compared to Standard Thromboprophylaxis

Author Year	Study Type	N	Baseline Severity	Length of Observation Period (days)	Adjustment	Results
Hazard Ratios						
Al-Samkari[18]	Cohort		Severe or critical	27#	Baseline severity and covariates	HR=1.12 (95% CI [0.92-1.36])
Jonmarker[3]	Cohort	152	Severe or critical	28	Baseline severity and covariates	HR=0.33 (95%CI [0.13-0.87])
Vaughn[19]	Cohort	1351	Mixed	60	Baseline severity and covariates	HR=1.31 (95%CI [0.99-1.73])
Odds Ratios						
Canoglu[20]	Cohort	154	Mixed	NR	Baseline severity and covariates	OR= 6.495 (95%CI [2.393-17.627])
Copur[21]	Cohort	115	Mixed	11.9#	Baseline severity and covariates	OR=2.187 (95%CI [0.484-9.880])
Ferguson[22]	Cohort	141	Severe or critical	28	Covariates	OR=0.73 (95%CI [0.33-1.76])
Jiménez-Soto[8]	Cohort	321	Mixed	NR	Baseline severity and covariates	OR=0.63 (95%CI [0.16-2.46])
Kumar[9]	Cohort	4645	Mixed	NR	Baseline severity and covariates	OR=0.47 (95%CI [0.27-0.80])
Sholzberg[23]	RCT	465	Moderate	28	Baseline severity and covariates	OR=0.22 (95%CI [0.07-0.65])
Risk Ratios						
Hsu[7]	Cohort	441	Mixed	30	Baseline severity and covariates	RR=1.05 (95%CI [0.55-2.02])%
Motta[24]	Cohort	133	Severe or critical	NR	Baseline severity and covariates	RR=2.40 (95%CI [0.90-6.60])
Lopes[25]	RCT	614	Mixed	30	None (randomized)	RR=1.49 (95%CI [0.90-2.46])
Patel[26]	Cohort	1716	Mixed	NR	Covariates	RR=5.93 (95%CI [3.71-9.47])
Spyropoulos[27]	RCT	257	Mixed	30	None (randomized)	RR=0.78 (95%CI [0.49-1.23])*
Proportion Comparison (therapeutic anticoagulation vs standard-dose thromboprophylaxis, p-value if reported)						
Elmelhat[28]	Cohort	59	Mixed	21.42#	None	3/39 (8%) vs 0/20 (0%), *p*=0.54
Gabara[14]	Cohort	201	Severe or critical	100	None	8/29 (28%) vs 17/78 (22%)
Goligher[29]	RCT	1074	Severe or critical	90	Baseline severity and covariates	199/534 (37%) vs 200/564 (35%)*

Author Year	Study Type	N	Baseline Severity	Length of Observation Period (days)	Adjustment	Results
Helms[30]	Cohort	179	Severe or critical	10^	None	20/108 (19%) vs 11/71 (15%)*
Kuno[31]	Cohort	766	Mixed	NR	Baseline severity and covariates	138/383 (36%) vs 115/383 (30%)
Lawler[32]	RCT	2219	Moderate	90	None (randomized)	86/1171 (7%) vs 86/1048 (8%)*
Lemos[33]	RCT	20	Severe or critical	28	None (randomized)	1/10 (20%) vs 3/10 (0%), *p*=0.26
Lynn[34]	Cohort	402	Mixed	NR	None	34.8% vs 15.2%
Qin[35]	Cohort	749	Mixed	28	None	25/77 (32%) vs 19/109 (17%)
Yu[36]	Cohort	348	Mixed	NR	Baseline severity and covariates	80/133 (60%) vs 131/215 (61%)

Notes.
Mean observation length
^ Median observation length
% Analytical sample is n=265 participants with no explanation for exclusions
*Comparator combines standard- and intermediate-dose anticoagulation
** Hemorrhage resulting in a decrease in hemoglobin greater than 2 g/dL with transfusion requirements, or a clinically significant decrease in platelet count (based on judgement of treating provider)

Thrombotic Events in Hospitalized COVID-19 Patients Receiving Intermediate-dose Anticoagulation Compared to Standard-dose Thromboprophylaxis

Author	Study Type	N	Outcome	Results
Hazard Ratio				
Bikdeli[1]	RCT	562	VTE	HR=0.93 (95% CI [0.48-1.76])
Martinelli[4]	Cohort	278	VTE	HR=0.52 (95% CI [0.26–1.05])
Moll[15]	Cohort	94	VTE	HR=2.0 (95% CI [0.8–5.2], *p* = 0.2)
Tacquard[6]	Cohort	538	TE	HR=0.79 (95% CI [0.65-0.95], *p*=0.014)
Odds Ratio				
Atallah[37]	Cohort	188	TE	OR=0.2 (95% CI [0.06-0.69], *p* = 0.01)
Avruscio[38]	Cohort	85	VTE	OR=0.6 (95% CI [0.3-1.4], *p* = 0.48)
Kumar[9]	Cohort	4645	VTE	OR=1.15 (95% CI [0.30 - 4.38]), *p* = 0.83)
Perepu[2]	RCT	173	VTE	OR=1.79 (95% CI [0.51–6.25], *p* > 0.99)
Taccone[39]	Cohort	40	PE	OR=0.09 (95% CI [0.02–0.57], *p* = 0.01)
Proportion Comparison (intermediate-dose anticoagulation vs standard-dose thromboprophylaxis, p-value if reported)				
Arachchillage[13]	Cohort	171	TE	9/110 (8%) vs 15/61 (25%), *p* = 0.005
Benito[40]	Cohort	76	PE	2/6 (33%) vs 26/60 (43%)
Gabara[14]	Cohort	201	VTE	21/94 (22%) vs 14/78 (18%)
Hsu[7]	Cohort	468	VTE	1/16 (6%) vs 18/337 (5%)
Jiménez-Soto[8]	Cohort	321	PE	1/135 (<1%) vs 2/109 (2%)
Jonmarker[3]	Cohort	152	TE	9/48 (19%) vs 12/67 (18%)
Lavinio[10]	Cohort	852	TE	No difference, *p* = 0.4
Pieralli[41]	Cohort	227	DVT	7/52 (13%) vs 18/130 (14%)
Stessel[12]	Cohort	72	VTE	19/46 (41%) vs 4/26 (15%), *p* = 0.03
Voicu[17]	Cohort	93	DVT	1/25 (2%) vs 11/42 (22%), *p* = 0.02
Zermatten[42]	Cohort	100	VTE	4.9 vs 18.5 per 1000 ICU-days; *p* = 0.04

Abbreviations. CI=confidence interval; DVT=deep vein thrombosis; HR=hazard ratio; ICU=intensive care unit; PE=pulmonary embolism; OR=odds ratio; RCT=randomized control trial; TE=thrombotic events; VTE=venous thromboembolism.

Thrombotic Events in Hospitalized COVID-19 Patients Receiving Therapeutic Anticoagulation Compared to Standard Thromboprophylaxis

Author	Study Type	N	Outcome	Results
Odds Ratio or Risk Ratio				
Atallah[37]	Cohort	188	TE	OR=0.4 (95% CI, [0.08-1.86], *p* = 0.24)
Helms[30]	Cohort	179	TE	OR=0.38 (95% CI, [0.14–0.94], *p* = 0.04)
Kumar[9]	Cohort	4,645	VTE	OR=1.30 (95% CI [0.57 - 2.95], *p*=0.52)
Lopes[25]	RCT	615	TE	RR=0.75 (95% CI, [0.45–1.26], *p* = 0.32)
Sholzberg[23]	RCT	465	TE	OR=0.29 (95%CI, [0.06-1.42])
Spyropoulos[27]	RCT	253	TE	RR=0.37 (95%CI [0.21-0.66], *p* <.001)
Proportion Comparison (therapeutic-dose anticoagulation vs standard-dose thromboprophylaxis, p-value if reported)				
Lawler, 2021 [32]	RCT	2219	Any thrombotic event	16/1180 (1.4%) vs 28/1046 (2.7%)
Goligher, 2021 [29]	RCT	1074	Any thrombotic event	38/530 (7.1%) vs 62/559 (11.1%)
Gabara[14]	Cohort	201	VTE	6/29 (21%) vs 14/78 (18%)
Hsu[7]	Cohort	468	VTE	5/48 (10%) vs 18/337 (5%)
Jiménez-Soto[8]	Cohort	321	PE	2/77 (3%) vs 2/109 (2%)
Jonmarker[3]	Cohort	152	TE	1/37 (3%) vs 12/67 (18%)
Lemos[33]	RCT	20	TE	2/10 (20%) in both groups
Motta[24]	Cohort	374	TE	9/75 (12%) vs 4/299 (1%), *p* = <0.01
Pieralli[41]	Cohort	227	DVT	6/45 (13%) vs 18/130 (14%)
Vaughn[19]	Cohort	1351	60-day VTE	32/219 (15%) vs 16/970 (2%)

Abbreviations. CI=confidence interval; DVT=deep vein thrombosis; PE=pulmonary embolism; OR=odds ratio; RCT=randomized controlled trial; RR=risk ratio; TE=thrombotic events; VTE=venous thromboembolism.

Bleeding Events in Hospitalized COVID-19 Patients Receiving Intermediate-dose Anticoagulation Compared to Standard Thromboprophylaxis

Author Year	Study Type	N	Baseline Severity	Outcome	Adjustment	Results
Hazard Ratios						
Bikdeli[1]	RCT	562	Severe or critical	Major bleeding	Treatment site	HR=1.82 (95%CI [0.53-6.24])
Halaby[43]	Cohort	433	Severe or critical	Major bleeding	Baseline severity and covariates	HR=0.78 (95%CI [0.34-1.78])
Pesavento[16]	Cohort	324	Moderate	Major or clinically relevant bleeding	Covariates	HR=3.89 (95%CI [1.90-7.97])
Odds Ratios						
Lavinio[10]	Cohort	852	Severe or critical	Critical hemorrhage*	Baseline severity and covariates	Log odds=0.189 (95%CI [-0.68-1.06])**
Perepu[2]	RCT	176	Severe or critical	Major bleeding	None (randomized)	OR=0.99 (95%CI [0.14-7.14])
Gabara[14]	Cohort	201	Severe or critical	Any bleeding	Baseline severity and covariates	OR=3.10 (95%CI [0.94-10.45])
Proportion Comparison (intermediate-dose anticoagulation vs standard-dose thromboprophylaxis, p-value if reported)						
Atallah[37]	Cohort	188	Severe or critical	Major bleeding	None	2/75 (3%) vs 6/83 (7%)
Arachchillage[13]	Cohort	171	Mixed	Major bleeding	None	8/110 (7%) vs 3/61 (5%)
Avruscio[38]	Cohort	85	Mixed	Major bleeding	None	1/26 (4%) vs 0/59 (0%)
Hsu[7]	Cohort	441	Mixed	WHO scale 1-4 bleed	None	1/16 (6%) vs 18/377 (5%)
Jiménez-Soto[8]	Cohort	321	Mixed	Major or clinically relevant bleeding	None	3/135 (2%) vs 7/109 (6%)
Jonmarker[3]	Cohort	152	Severe or critical	WHO scale 1-4 bleed	None	7/48 (15%) vs 8/67 (12%)
Kessler[44]	Cohort	270	Mixed	Major bleeding	None	3/183 (2%) vs 0/22 (0%)
Martinelli[4]	Cohort	278	Mixed	Major or clinically relevant bleeding	None	4/127 (3%) vs 0/151 (0%)
Moll[15]	Cohort	94	Severe or critical	Major bleeding	Baseline and covariates	5/47 (11%) vs 2/47 (4%)
Paolisso[11]	Cohort	450	Mixed	Major bleeding	None	2/89 (2%) vs 2/361 (1%)
Pieralli[41]	Cohort	227	Moderate	Major hemorrhagic complication	None	0/52 (0%) vs 0/130 (0%)

Author Year	Study Type	N	Baseline Severity	Outcome	Adjustment	Results
Taccone[39]	Cohort	40	Severe or critical	Any hemorrhagic complication	None	3/12 (25%) vs 2/22 (9%)
Voicu[17]	Cohort	93	Severe or critical	Major bleeding	None	11/42 (26%) vs 7/50 (14%)

Notes.
*Critical hemorrhage defined as intracranial hemorrhage or bleeding requiring red blood cells transfusion.
** Analysis reports unscaled log odds instead of odds ratio; a value >0 (including <1) indicates survival benefit of intermediate prophylaxis.

Bleeding Events in Hospitalized COVID-19 Patients Receiving Therapeutic Anticoagulation Compared to Standard Thromboprophylaxis

Author Year	Study Type	N	Baseline Severity	Outcome	Adjustment	Results
Hazard Ratios						
Halaby[43]	Cohort	433	Severe or critical	Major bleeding	Baseline severity and covariates	HR=1.55 (95%CI [0.88-2.73])
Odds Ratios						
Gabara[14]	Cohort	201	Severe or critical	Any bleeding	Baseline severity and covariates	OR=5.93 (95%CI [1.55-22.72])
Goligher[29]	RCT	1074	Severe or critical	Major bleeding	Baseline severity and covariates	OR=1.48 (95%CI [0.75-3.04])*#
Lawler[32]	RCT	2219	Moderate	Major bleeding	Baseline severity and covariates	OR=1.80 (95%CI [0.90-3.74])*%
Sholzberg[23]	RCT	465	Moderate	Major bleeding	Baseline severity and covariates	OR=0.52 (95%CI [0.09-2.85])
Risk Ratios						
Lopes[25]	RCT	614	Mixed	Any bleeding	None (randomized)	RR=3.92 (95%CI [1.92-8.00])
Spyropoulos[27]	RCT	257	Mixed	Major bleeding	None (randomized)	RR=2.88 (95%CI [0.59-14.02])*
Proportion Comparison (therapeutic anticoagulation vs standard-dose thromboprophylaxis, p-value if reported)						
Atallah[37]	Cohort	188	Severe or critical	Major bleeding	None	5/24 (21%) vs 6/83 (7%)
Elmelhat[28]	Cohort	59	Mixed	Any bleeding	None	3/39 (8%) vs 0/20 (0%), *p*=0.54
Ferguson[22]	Cohort	141	Severe or critical	Requirement of packed red blood cell transfusion for a hemoglobin <7 g/dL	None	12/46 (26%) vs 8/95 (8%)
Helms[30]	Cohort	179	Severe or critical	WHO scale 3 or 4 bleed	None	2/108 (2%) vs 1/71 (1%)*
Hsu[7]	Cohort	441	Mixed	WHO scale 1-4 bleed	None	5/48 (10%) vs 18/377 (5%)
Jiménez-Soto[8]	Cohort	321	Mixed	Major or clinically relevant bleeding	None	12/77 (16%) vs 7/109 (6%)
Jonmarker[3]	Cohort	152	Severe or critical	WHO scale 1-4 bleed	None	1/37 (3%) vs 8/67 (12%)
Kessler[44]	Cohort	270	Mixed	Major bleeding	None	11/65 (17%) vs 0/22 (0%)
Lemos[33]	RCT	20	Severe or critical	Any bleeding	None	2/10 (20%) vs 0/10 (0%)

Author Year	Study Type	N	Baseline Severity	Outcome	Adjustment	Results
Lynn[34]	Cohort	402	Mixed	Hemorrhage	None	9% vs 3%
Pieralli[41]	Cohort	227	Moderate	Major hemorrhagic complication	None	2/45 (4%) vs 0/130 (0%)
Yu[36]	Cohort	348	Mixed	Major bleeding	Baseline severity and covariates	18/133 (14%) vs 8/215 (4%)

Notes.
*Comparator combines standard- and intermediate-dose anticoagulation
** Hemorrhage resulting in a decrease in hemoglobin greater than 2 g/dL with transfusion requirements, or a clinically significant decrease in platelet count (based on judgement of treating provider)
# Some patients missing bleeding outcome (n=47 therapeutic anticoagulation group and n=50 standard-dose anticoagulation group)
% Some patients missing bleeding outcome (n=1 therapeutic anticoagulation group and n=3 standard-dose anticoagulation group)

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Quality Assessment of Randomized Control Trials Based on the Cochrane ROB-2 Tool

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
Goligher, 2021[29] (ATTACC/ACTIV-4a/REMAP-CAP)	Unclear Response Adaptive Randomization within strata used for REMAP-CAP and ATTACC; allocation sequence was concealed. 1:1 randomization within strata used for ACTIV-4; unclear if allocation sequence was concealed. Randomization appears effective (baseline characteristics balanced).	Low Study had open label design--both participants and carers knew dosage received, but outcomes were unlikely to have been affected by knowledge of the intervention. 10/590 in intervention group and 15/615 in the control group withdrew consent after randomization, so deviation from assignment was low.	Unclear Study was open label, but patients were hospitalized and unlikely to have access to alternative interventions. Dosage received info only available for 83% of participants, but missing dosages are balanced between groups. Only 7.4% of control group escalated to sub-therapeutic or therapeutic dosage--much more frequent for therapeutic group to de-escalate	Low Outcome data only missing for 1.2% of randomized patients. Consent withdrawn for 2.1%. COVID-19 not confirmed for 7.6% of cohort.	Low Data was abstracted from medical records and unlikely to be influenced by knowledge of intervention; also adjudicated by blinded analysts	Low Authors report when analyses deviate from protocol and provide caution about interpretation	Some concerns	<80% adherence to assigned intervention	

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
			dosage (22.3%).						
Lawler, 2021[32] (ATTACC/ACTIV-4a/REMAP-CAP)	Unclear Response Adaptive Randomization within strata used for REMAP-CAP and ATTACC; allocation sequence was concealed. 1:1 randomization within strata used for ACTIV-4; unclear if allocation sequence was concealed. Randomization appears effective (baseline characteristics balanced).	Low Study had open label design--both participants and carers knew dosage received, but outcomes were unlikely to have been affected by knowledge of the intervention. 9/1190 in intervention group and 2/1055 in the control group withdrew consent after randomization, so deviation from assignment was low.	Unclear Study was open label, but patients were hospitalized and unlikely to have access to alternative interventions. Dosage received info only available for 88.3% of intervention group and 81.4% of control group. Only 1.7% of control group escalated to sub-therapeutic or therapeutic dosage--much more frequent for therapeutic group to de-escalate dosage (11.6%).	Low Only 1.2% missing outcome data	Low Data was abstracted from medical records and unlikely to be influenced by knowledge of intervention	Low Authors report when analyses deviate from protocol and provide caution about interpretation	Some concerns		
Bikdeli and Sadehipour, 2020[1,45]	Low Allocation sequence was	Low Study had open label	Unclear About 74% of participants	Low Outcome data appears to be	Low Outcome determinations	Low Reported results are	Low	Biggest concern is 26% who did	

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
(INSPIRATION)	concealed; block randomization. Randomization appears to have been successful based on baseline characteristics.	design--both participants and carers knew dosage received, but outcomes were unlikely to have been affected by knowledge of the intervention. 6% of the intervention and 4% of the control groups withdrew consent after randomization, so there does not appear to have been bias in assignment.	completed the treatment as planned. Reasons for deviation are not reported by intervention group, so it is difficult to assess risk of bias, but time spent on intended intervention appears balanced between groups.	complete for all randomized patients <5% of patients are missing baseline data.	were made by clinicians blinded to intervention status	clearly labeled as per-protocol/pre-specified and ad-hoc; results that were promised in protocol are reported		not complete interventions as planned and lack of reporting of deviation reason by intervention group. However, 90.1% spent at least 15 days on the planned dosage, and 83.2% stayed on planned dosage for at least 80% of 30 planned days. Time spent on planned intervention did not differ between intervention groups, and these time frames likely reflect real-world conditions.	

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
Lemos, 2020[33]	Low Block randomization concealed in opaque envelopes; no significant differences in important baseline characteristics.	Unclear No specific mention of blinding, but patients were on ventilators and unlikely to be aware of status, at least until removed from ventilator. Protocol allowed for changes in intervention due to renal function or bleeding events, but changes were not necessary. All participants were analyzed in group to which they were assigned.	Unclear No specific mention of blinding, but patients were on ventilators and unlikely to be aware of status, at least until removed from ventilator. Prone positioning, corticosteroids, *etc*, balanced between groups. All patients received intervention to at least 96 hours, though unclear after that time. Adherence was not dependent on participants; completed as planned in all participants; analyzed according to randomized	Low Outcomes available for all participants randomized	Unclear In-hospital mortality and 28-day mortality provided (in-hospital value likely more useful, as COVID-19 patients can have long hospitalizations); bleeding outcomes measured with standardized definition. Guidelines provided across groups; ascertained from medical records. Assessors were blind to blood gas analysis results, but no mention of blinding for other outcomes. Knowledge of intervention status unlikely to influence measurement of mortality or	Low Participants analyzed according to random-ization groups using prespecified techniques. Authors highlighted significant differences in intermediate outcomes in abstract and discussion, but all outcomes were analyzed and reported; no major deviations from published protocol.	Some concerns	Unclear risk of bias in differential care to patients based on intervention status (unclear if providers knew of assignment). Unclear potential for differential mis-classification of bleeding outcomes.	

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
			intervention groups.		ventilator-free day outcomes; possible it could have affected classification of bleeding events if they were aware of intervention status.				
Lopes, 2021[46] (ACTION)	Low Allocation sequence was concealed; block randomization. Randomization appears to have been successful based on baseline characteristics.	Low Study had open label design--both participants and carers knew dosage received, but outcomes were unlikely to have been affected by knowledge of the intervention. <1% of the intervention and 0% of the control groups withdrew consent after randomization; 0% of intervention and <1% of	Low Study was open label, but patients were hospitalized and unlikely to have access to alternative interventions. Mean 30-day adherence to assigned treatment was 94.8% in the intervention group and 99.5% in the prophylactic group.	Low Outcome data appears to be complete for >99% randomized patients.	Low Outcome determinations were made by independent committee blinded to intervention status.	Low Reported results appear to match pre-specified protocol.	Low	Potentially low applicability due to high rate of eligible patients declining to participate (269 declined, 615 agreed to random-ization).	

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
		control groups crossed over in dosage after assignment so there does not appear to have been bias in assignment.							
Perepu, 2021[2]	Low Patients were randomly assigned in a 1:1 ratio. The supplemental materials refer to a centralized web-based program for randomization, so it's unclear but likely that the allocation sequence was concealed. No significant differences in important baseline characteristics.	Low Study had open label design--both participants and carers knew dosage received, but outcomes were unlikely to have been affected by knowledge of the intervention. Deviations were fairly balanced between groups. 2% of the intervention and 1% of the control group participants withdrew consent after randomization.	Unclear Deviations were fairly balanced between groups. 1% of intervention and 3% of control group did not receive the intended treatment. Co-interventions were not balanced between groups.	Low Data are available for all patients in intention-to-treat analysis.	Low for mortality outcome and unclear for bleeding. Outcomes were adjudicated independently by 2 investigators who were not blinded; possible that thrombosis and bleeding outcomes classification could have been impacted by knowledge of the treatment.	Low Outcomes were reported for all participants as prespecified in the study protocol.	Some concerns	Unclear risk of bias due to unbalanced receipt of co-interventions (specifically azithromycin) between intervention and control groups, although the difference applied to only 20% of participants. Unclear risk of bias due to lack of blinding in outcome assessment.	The implications of unbalanced co-interventions for a subset of study participants is unclear because it is unknown which direction the co-intervention could have skewed results. Lack of blinding in outcome assessment would not have affected mortality but could have led to bias in

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
									classification of thrombosis and bleeding outcomes.
Sholzberg, 2021,[23] (RAPID)	Low Study used block randomization (stratified by age group and size) with allocated concealment. Groups appear balanced at baseline.	Low Study had open label design--both participants and carers knew dosage received, but outcomes were unlikely to have been affected by knowledge of the intervention as all patients were hospitalized. 97.4% of the therapeutic AC group and 97.9% of the standard (control) group received treatment as allocated during the first 48 hours after randomization.	Unclear Adherence after initial dose not reported. Treatment duration was 3.0-8.0 days for both intervention and control groups. Trial did not allow either group to received intermediate AC doses. Used intention to treat analysis.	Low Only 11/228 intervention and 12/237 control group patients were lost to follow up after discharge from hospital alive.	Low Researchers were blinded to intervention groups when adjudicating thrombotic and bleeding outcomes. Standard procedure used across groups.	Low Clearly identifies which analysis components were pre-specified in published protocol and appears to report all main per-protocol outcomes.	Low		

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
Spyropoulos, 2021 (HEP-COVID)[27]	Unclear Patients were randomly assigned in a 1:1 ratio. Unclear if the allocation sequence was concealed. ~12% more patients in the therapeutic dose group received glucocorticoids and ~10.5% more received antiplatelets prior to randomization.	Low Patients and investigators were blinded to treatment assignment as much as possible but the study does not indicate how often blinding was accomplished. Deviations were fairly balanced between groups. <1% of intervention and control group participants withdrew consent after randomization.	Low Deviations were fairly balanced between groups. <1% of intervention and 2% of control group did not receive the intended treatment.	Low Data are available for all patients in intention-to-treat analysis. Participants with missing data were excluded prior to random-ization.	Low Outcomes were adjudicated by blinded investigators using medical record data. All patients received DVT screening at similar time points.	Unclear There were many changes to the trial protocol. Though all of them are documented in the supplemental materials, the manuscript is not transparent about any of the changes except those to the inclusion and exclusion criteria. Several of the changes are to what qualifies as an outcome and were made late in the process. Whether the late changes actually affect the results of the	Some concerns	Unclear success of randomization	Higher proportion of patients in the therapeutic AC group that received co-interventions prior to random-ization could have resulted in overestimate of treatment benefits.

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of bias from Missing Outcome Data	Risk of bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)	What are the main limitation(s) of the study?	What are the implications of these limitations?
						primary analysis is unclear. The added outcomes are balanced between treatment groups--main impact is that more patients considered to have received per protocol treatment.			

Quality Assessment of Observational Studies Based on the ROBINS-I Tool (Columns a-e)

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
Al-Samkari, 2021[18]	Low Consecutive patients during specified timeframe. Patients received intervention within 2 days of ICU admittance.	Low Interventions prespecified and clearly defined and recorded at baseline.	Unclear Unclear adherence and/or deviations from interventions. Some patients not receiving therapeutic AC may have initiated therapeutic AC after 2 days.	VTE: Unclear Mortality and bleeding: Low VTE events were screened when clinically suspected (though not always suspected) Objective outcome of death recorded in medical records.	VTE and bleeding: Low Mortality: Unclear Analysis adjusted for multiple variables, including demographics and disease characteristics. Analysis doesn't adjust for corticosteroids, which increases the likelihood mortality estimates would be biased due to confounding.
Arachchillage, 2021[13]	Low AC was initiated at admission; all patients with confirmed COVID were included	High The intervention AC regimen spans standard prophylaxis to therapeutic AC depending on the weight and D-dimer level of patients It is unclear why some received standard prophylaxis when weight/D-dimer adjusted was recommended.	Unclear Adherence is not reported. Co-interventions not reported by AC group.	VTE: Unclear Mortality and bleeding: Low Patients on standard AC were more likely to received screening for VTE, but test positivity rates were balanced between groups Mortality and bleeding assessments were unlikely to be influenced by knowledge of intervention group	High No adjustment is made for confounding factors. May be some factors associated with not receiving the adjusted dosage that influence outcome.
Atallah, 2020[37]	Unclear Patients in ICU for <24 hours were excluded. No comparison of patient characteristics between intervention dosages.	Low Groups clearly defined by dosage/intervention assigned at or near ICU admission.	Unclear Dosage changed if patients had clinical suspicion of VTE; unclear if rising D-dimers or other criteria also led to escalation of dosage	Unclear Imaging/screening for VTE was provided only to patients with high D-dimers or clinical suspicion of VTE. Outcome screening may	Unclear AC dosages were based on baseline risk of outcome (confounding by indication). Potential for residual confounding, as there is no adjustment for comorbidities or age. Unclear if multivariate

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
				have differed across intervention groups.	analysis adjusts for factors observed at baseline or after the intervention started.
Avruscio, 2020[38]	Low Consecutive patients enrolled, AC started on admission.	Low Groups clearly defined, prescribed on admission	Unclear All patients received thromboprophylaxis as prescribed, but unclear balance of co-interventions	DVT or Death with VTE: Low PE: Unclear Patients were only screened for PE if symptomatic/clinically suspected; PE can present unusually in COVID patients, so it's possible screening and detection were differential.	Unclear Adjusted for multiple baseline variables, including demographics and comorbidities, but unclear which analyses were adjusted for which variables. Multivariate analysis provided in supplemental materials (table S2); considered many adjusting variables, but not clear why only 3 were included.
Benito, 2020[40]	High Selection of patients depended on suspicion of outcome, which was also likely associated with the intervention (those with clinical suspicion may be more likely to have increased doses).	Unclear The hospital guidance to start prophylactic doses on all patients started after the start date of the study and then guidance for increased doses was near the end of the study period. This means the classification likely had to happen after the start of the study.	High Intensity of dosage for some participants was switched partway through study period, and changes were based on lab results and risk factors correlated with outcome.	Unclear Though the decision to seek an outcome measurement could have been influenced by knowledge of intervention, the measure itself was based on imaging unrelated to the intervention. Although providers assessing imaging results likely knew the intervention status, unlikely to have influenced assessment of PE.	High Strong potential for confounding by indication (*ie*, providers prescribed AC at higher dosages for patients with comorbidities or early risk factors for outcome). Authors did not adjust for confounding.
Canoglu, 2020[20]	Unclear Appears to be all patients hospitalized	Unclear Interventions clearly defined. Unclear timing	Unclear Unclear adherence and/or deviations from interventions. All	Low	Low Analysis adjusted for multiple variables, including

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	with severe COVID-19 during a specific timeframe. Unclear balance of baseline characteristics between intervention groups. Unclear if patients started therapeutic or prophylactic AC doses within a similar timeframe. Excluded patients with hospital stay <5 days, which might have differentially excluded people who received early intervention and responded positively to it, though it also might have appropriately excluded people with moderate pneumonia.	of classification (*ie*, if a patient may have received both dosages during hospital stay).	patients received antiviral and supporting treatment.	Objective outcome of death recorded in medical records.	demographics and disease characteristics.
Copur, 2021[21]	Unclear All adults with COVID-19 who received LMWH for at least 3 days were included. Unclear if bias could result from excluding those who received LMWH for less than 3 days or other forms of AC.	Low Intervention groups are clearly defined.	Unclear Deviations from interventions not reported. Co-interventions appear balanced.	Low	Unclear Adjusted for some relevant covariates in multivariable model but not use of corticosteroids or other co-interventions.
Elmelhat, 2020[28]	Unclear	Unclear	Unclear	Unclear	High

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
	Consecutive patients during a specified timeframe. Baseline characteristics mostly balanced between intervention groups. Unclear if patients started different AC doses within a similar timeframe.	Consecutive patients during a specified timeframe. Baseline characteristics mostly balanced between intervention groups. Unclear if patients started different AC doses within a similar timeframe.	Unclear adherence and/or deviations from interventions. Unclear co-interventions across groups.	Unclear timing of outcome assessment and unclear methods for outcome assessment. Objective outcome - death.	Does not appear to be adjustment for any confounders. Doses given likely based on risk, which influence outcome.
Ferguson, 2020[22]	Unclear Inclusion was conditioned on intubation, which occurred after the start of intervention(s). Unclear if AC dosage affected progression to intubation.	Unclear Therapeutic and prophylactic interventions both had wide ranges of possible dosages. It's possible the ranges overlapped, but unclear how many patients would fall in the overlap.	High There was a wide and ambiguous timeframe in which AC doses could have been administered ("before intubation"); possible that patients started on higher dose AC after changes in clinical course of disease. Classified prevalent users on AC prior to admission into therapeutic group and its unclear how long and what dosages they were on.	Low No mention of blinding outcome assessors to intervention status, but mortality is a clear outcome, reliably documented, and difficult to misclassify based on intervention status	Unclear Results are adjusted for co-interventions. Some control via restriction to critically ill/intubated population, but residual confounding likely present from comorbidities. Unclear which factors were included in adjustment.
Gabara, 2021[14]	Unclear Intervention category was assigned based on highest AC dosage received; intervention assignment could have been made for higher AC groups well after the start of follow up and systematically later than for the standard prophylaxis group.	Low Intervention groups are clearly defined. AC classification determined prior to assessment of VTE outcome.	Low It appears that all participants received the intended intervention.	Low for mortality and unclear for TE and bleeding. Diagnostic imaging was obtained based on clinical suspicion which could have been influenced by knowledge of AC status. Similarly, bleeding events may have been detected or recorded at higher rates given knowledge of AC status.	Unclear--adjusted for most relevant covariates in multivariable model but not use of corticosteroids or other co-interventions.

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
Halaby, 2021[43]	Unclear Appears to be all patients during a specific timeframe. Unclear balance of baseline characteristics between intervention groups. Unclear if patients started different AC doses within a similar timeframe.	Low Interventions clearly defined. AC doses classified as highest received in 24 hours. Time-varying AC dosage investigated.	Unclear Unclear adherence and/or deviations from interventions. Unclear co-interventions across groups.	Low Bleeding events assessed for all patients, confirmed by independent investigator.	Low Adjusted for multiple variables, including patient and disease characteristics.
Helms, 2021[30]	Unclear All patients during a specific timeframe. Generally balanced characteristics between intervention groups. Unclear if patients started different AC doses within a similar timeframe.	Low Interventions clearly defined. Patients switching from prophylactic to therapeutic AC were analyzed as "prophylactic".	Unclear Unclear adherence and/or deviations from interventions. Unclear co-interventions across groups.	VTE: High Mortality and bleeding: Low The rate of screening for VTE generally increased over time with awareness of COVID's role in clotting, which is also what drove changes in AC recommendations that participating centers followed. Mortality and bleeding events were clearly documented and unlikely to be misclassified by intervention status	Unclear Adjusted for multiple variables, including patient and disease characteristics. Aspects of care for COVID patients changed a lot over time, and study did not attempt to adjust for many differences in care.
Hsu, 2020[7]	Low Included all patients admitted with COVID-19 in health system included	Unclear New AC dosage guidelines were implemented during study period - unclear	Unclear Changes in AC dosage not reported/described; co-interventions not reported (most	VTE: High Mortality and bleeding: Low Imaging to diagnose VTE events only done when	Unclear Confounding by indication possible; dose based on D-dimers/baseline risk of outcome (patients on higher

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
		how patients were categorized or if categories changed	important for mortality to know steroid treatment)	clinically suspected; as AC dosage was based on labs/risk factors for VTE, imaging was more likely to be ordered among patients on intermediate prophylaxis or therapeutic dose AC	intensity AC more likely to develop outcomes). Many variables differed between groups at baseline, and it is unclear if authors adjusted for them all under the "COVID-19 severity indicators" adjustment.
Jimenez-Soto, 2020[8]	Unclear All patients during a specific timeframe. Some differences in baseline characteristics between intervention groups. Unclear if patients started different AC doses within a similar timeframe.	Unclear Interventions clearly defined. Unclear timing of classification (*ie*, if a patient may have received multiple dosages during hospital stay).	Unclear Unclear adherence and/or deviations from interventions. Unclear co-interventions across groups.	VTE: High Mortality: Low Objective outcome of death recorded in medical records. Not all patients received screening for thrombotic events.	Unclear Adjusted for multiple variables, including patient and disease characteristics, but not for co-interventions.
Jonmarker, 2020[3]	Low All critically ill patients admitted during study period were eligible. Exclusions were made for limited baseline characteristics or discharge within 24 hours of ICU admission.	Low Classification based on initial dosage documented in medical records on day of admission to ICU. Clear distinction between dosage categories, though cut offs may be arbitrary (unclear if AC medications were prescribed on a continuum or at consistent dosages within specified categories)	Unclear 42.1% of patients increased and 3.3% of patients decreased dosages (median 4 [2-7] days after ICU admission). Sensitivity analysis barely changed multivariate HR estimate of high vs low dose barely changed. Swung from HR 0.88 to 1.15 for medium vs low dose.	Mortality and bleeding: Low VTE: Unclear Criteria for imaging for VTE unclear/not described, and probability of receiving imaging may have been associated with AC dosage. Mortality and bleeding clearly defined, abstracted from medical records, and reviewed by at least 2 doctors.	Unclear Important confounders (time of admission, glucocorticoids/ co-interventions) left out of main analysis. Included in separated sensitivity analyses. Inclusion of glucocorticoids did not substantially change results, but when median admission time was included in the model, the HR of mortality high vs low AC dosage shifted toward the null value and was no longer statistically significant.

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Kessler, 2020[44]	Unclear All patients at the hospital with lab-confirmed COVID-19 were eligible and included in study No comparison of baseline characteristics between intervention groups.	Unclear Intervention levels changed in 27% of patients and it's unclear how they were classified in the analysis.	High Intervention levels changed in 27% of patients. No information provided on co-interventions.	Unclear No mention is made of methods for evaluating/ assessing outcome (*eg*, dual record review, blinding, *etc*).	High No comparison of differences in characteristics between intervention groups. Authors did not adjust or control for confounding variables (*ie*, age, co-interventions, and comorbidities).
Kumar, 2021[9]	Low All adults with PCR-confirmed SARS-CoV-2 hospitalized during the study period were included.	Low Intervention groups are clearly defined. AC classification determined prior to assessment of VTE outcome.	Unclear Deviations from interventions not reported; co-interventions appear mostly, though not completely balanced.	Low for mortality and unclear for TE and bleeding. Diagnostic imaging was obtained based on clinical suspicion which could have been influenced by knowledge of AC status. Similarly, bleeding events may have been detected or recorded at higher rates given knowledge of AC status.	Unclear No information provided regarding choice of AC. Study adjusted for IPTW weights, but it's difficult to assess risk of residual confounding when dosage guidelines are not provided.
Kuno, 2021[31]	Low Timing of AC among all included patients was within 2 days of admission.	Unclear Medications, but not dosages, are specified.	Unclear Deviations from interventions not reported. Co-interventions appear balanced in propensity-matched model.	Low	Unclear No information provided regarding choice of AC.
Lavinio, 2021[10]	Low Includes consecutive patients at participating centers. Appears that AC regimens were	Unclear Some patients categorized by dose received, while others were classified by anti-	Unclear No discussion of adherence to AC regimen. Antiplatelet use is balanced across groups.	Low Does not appear that outcome assessors were blinded to intervention status, but bleeding event	Low PSM modes adjusted for important confounders, including baseline security and antiplatelet use.

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
	selected at or near ICU admission.	Xa activity, but this is not uncommon in the field. Some patients may have received AC in the therapeutic range, but most received intermediate doses.		were unlikely to be affected by knowledge of intervention.	
Lynn, 2021[34]	Unclear It appears selection into the study was all patients during a specific time period. However, it is unclear if the start of intervention was similar across patients (it appears it was at admission but no specific timeframe of initiating AC was reported)	Unclear Based on medical records, but only therapeutic AC dosage is defined; prophylactic AC could encompass a very wide range	Unclear Patients in general/medicine wards were generally treated if D-dimer ever exceeded 3 micro-grams/mL during daily monitoring; no description of when in the hospitalization patients were escalated to therapeutic AC.	Low In-hospital mortality was clearly documented and unlikely to be misclassified by intervention status	Unclear Adjusted for many important confounders, but did not adjust for timing of admission or use of corticosteroids
Martinelli, 2021[4]	Unclear It appears selection into the study was all patients during a specific time period. However, it is unclear if the start of intervention was similar across patients (it appears it was at admission, but no specific timeframe of initiating AC was reported)	Low Categories were clearly defined and documented in medical records	Unclear Analysis appears to follow initial treatment with clinical deterioration used as an outcome in ICU and high intensity of care wards, but low-intensity ward patients could have started on lower dose and escalated later based on SOFA score.	In-hospital mortality and bleeding: Low VTE: high VTE outcomes: only screened when clinically suspected, more likely to be suspected in patients with higher SOFA scores (which were tied to intervention for some patients) Mortality and bleeding events were clearly documented and unlikely	Unclear Adjusted for many important confounders, but did not adjust for timing of admission or use of corticosteroids

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
				to be misclassified by intervention status	
Meizlish, 2021[5]	Unclear Selection into the study was all patients during a specific time period. However, it is unclear if the start of intervention was similar across patients.	Low Documented with clear (if not recommended; see departure from interventions) criteria for selecting category	Unclear Patients categorized based on highest dose received; likely that some patients started on standard prophylaxis, worsened, and escalated to high-dose prophylaxis	Low In-hospital mortality was clearly documented and unlikely to be misclassified by intervention status	Unclear Adjusted for many important confounders but did not adjust for use of corticosteroids. D-dimer levels were not balanced in final propensity score model.
Moll, 2021[15]	Low Study appears to enroll all patients eligible during study period. Doses were administered at the start of ICU admission.	Low Categories were clearly defined and documented in medical records	Unclear Deviations from interventions not reported.	VTE: High Mortality and bleeding: Low VTE outcomes: No specific protocol for screening was in place; likely increased over time with awareness of coagulation (study period early in the pandemic, and intermediate AC not provided until partway through the study period). Those on intermediate AC likely had higher probability of VTE screening Mortality and bleeding events were clearly documented and unlikely to be misclassified by intervention status	High Early patients had no chance of intermediate prophylaxis, and time of admission early in the pandemic correlated with improved care and outcomes. The study corrected for some confounding by indication with propensity scores (matched on severity and other risk factors) but by definition could not address time trends. Cohorts were not completely balanced on severity factors even after matching. No adjustment/matching for steroid treatment. Patients were matched for length of stay, which may have over adjusted/removed treatment effect (if present).
Motta, 2020[24]	Low All eligible patients during the study period	Low Documented with clear (if not recommended;	Unclear Patients categorized based on highest dose received; likely that	Low In-hospital mortality was clearly documented and	Unclear AC intensity was likely influenced by disease

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
	were included, and AC was initiated at admission.	see departure from interventions) criteria for selecting category	some patients started on standard prophylaxis, worsened, and escalated to high-dose prophylaxis, though sensitivity analysis using dosage at admission did not change conclusions	unlikely to be misclassified by intervention status	severity/predictors of the outcome; PSM model matched patients on severity, but it's unclear how well balanced the model was or whether severity measurements came from baseline or whole hospitalization. Adjusted for many important confounders but did not adjust for use of corticosteroids.
Paolisso, 2020[11]	Low Patients would have been excluded for having hospital stay <5 days, but none were excluded for this reason; all other exclusions were based on pre-intervention characteristics. Not reported at what point in hospitalization intervention started; intervention lasted consistent length	Low Clear distinction between prophylactic and intermediate dosing. Recorded in medical records.	Unclear 26 patients excluded for receiving full therapeutic dose heparin, but it's unclear if they started at a different dosage. Hydroxychloroquine and tocilizumab more frequently administered to patients in intermediate dose group, but co-interventions unlikely to have had impact.	Low All-cause mortality not high risk for differential measurement.	Low Strong potential for confounding and confounding by indication; dosage decisions left to clinician discretion. However, authors controlled for age, hypertension, baseline parameters, and co-interventions in propensity score model.
Patel, 2020[26]	Unclear Timing of interventions not known and likely may not have aligned for most patients.	Unclear No reporting on distribution of time from point of hospitalization to treatment with AC	Unclear Patients categorized based on highest dose received; likely that some patients started on standard prophylaxis, worsened, and escalated to high-dose prophylaxis	Low In-hospital mortality was clearly documented and unlikely to be misclassified by intervention status	Unclear Adjusted for many important confounders but did not adjust for use of corticosteroids. Adjustment for confounders may not be sufficient to account for differences between groups.

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
Pesavento, 2020[16]	Low Enrolled consecutive patients with COVID-19; some exclusions, but all based on baseline characteristics (*eg*, need for ICU at baseline, chronic treatment with vitamin K antagonists)	Low Dosage ranges were clear, and prescriptions abstracted from medical records	Unclear Classification was based on drug treatments across hospital stay, not just regimen assigned at/near admission; no description of whether patients stayed on consistent regimen or changed dosages	All-cause mortality and bleeding: Low VTE: Unclear Mortality assessment unlikely to be impacted by knowledge of intervention; bleeding outcomes assessed using clear, standard definition and recorded in medical records. VTE assessed based on abstraction from medical record diagnoses, but otherwise undescribed	Unclear Potential for residual confounding (other medications, indication for AC, *etc*), but there is adjustment for some of the major factors.
Pieralli, 2021[41]	Low Included all consecutive patients at participating hospitals. AC provided at admission.	Low Categories were clearly defined and documented in medical records	Unclear Deviations from assigned intervention not reported.	VTE: Unclear Mortality: Low All patients underwent ultrasound, but CTPA only performed for patients with clinical suspicion. No mention of blinding of outcome assessors. Mortality was clearly documented and unlikely to be misclassified by intervention status	High Criteria for determining which level of AC patients received is not specified--likely that severity of disease contributed. No assessment of differences between intervention groups and likely differed by disease factors influencing outcome. Variables in adjusted model not reported, except for peak D-dimer (which is an inappropriate include).
Qin, 2021[35]	Low All patients during a given timeframe were included, and AC was started upon admission or within 7 days.	Unclear Median time from hospitalization to intervention initiation was 3 days; median survival time for those	High 19/109 patients starting on prophylactic AC switched to therapeutic AC; protocol states all patients received methyprednisone, but only 21%	Low 28-day mortality was clearly documented and unlikely to be misclassified by intervention status	High Adjusted model only compares AC yes/no, not therapeutic vs standard AC

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
		who died was 8.5, so initiation could very well have followed clinical deterioration	were treated with corticosteroids, and corticosteroid use was not balanced between groups		
Stessel, 2020[12]	Unclear All patients admitted during a specific time period were selected into the study. However, it is unclear if the start of intervention was similar across patients (appears to be at admission, but not clear).	Low Categories were clearly defined and documented in medical records	Unclear Deviations from interventions not reported; co-interventions appear mostly, though not completely balanced	VTE: High Mortality: Low Onset of twice weekly DVT screening started at same time as initiation of therapeutic AC. Mortality was clearly documented and unlikely to be misclassified by intervention status	Unclear Adjusted for many important confounders, but could not adjust for timing of admission
Taccone, 2020[39]	Unclear Time from start of follow up to outcome measurement is recorded, but not start of follow up to start of intervention. Three patients excluded for early death and 6 for rapid improvement; these patients did not have CTPA and represented <20% of population	Low Clear distinction in dosages. Medical records documented interventions when they started.	Unclear Initial dosages clear between groups, but methods state that anti-Xa was used to monitor AC, and dosages were adjusted as needed to hit target range; unclear whether adjustments would have been extreme enough to blur intervention groups.	Unclear Outcome measured by imaging; all patients screened. Imaging reviewed by one radiologist at time they were taken, no mention of blinding to AC dose.	Low Multivariate model adjusted for age, co-morbidities, and relevant labs at baseline; may have resulted in over adjustment given small sample size.
Tacquard, 2021[6]	Unclear All patients admitted during a specific time period were selected into the study. However, it is unclear if	Unclear Some patients categorized by dose received, while others were classified by anti-	High AC was treated as a time-varying intervention, and many patients who started on standard prophylaxis escalated to therapeutic AC based on risk	VTE: High Mortality and bleeding: Low VTE outcomes: No specific protocol for screening was in place;	Unclear Adjusted for many important confounders, but did not adjust for timing of admission or use of corticosteroids

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
	the start of intervention was similar across patients (appears to be at admission, but not clear).	Xa activity, but this is not uncommon in the field	factors (some time-varying and precursors of outcomes)	likely increased over time with frequency of therapeutic AC Mortality and bleeding events were clearly documented and unlikely to be misclassified by intervention status	
Vaughn, 2021[19]	Unclear Either included all eligible patients from center or daily random sample based on minute of discharge for centers with insufficient DA capacity for full abstraction of all patients Assignment to intervention groups was based on actual AC received over the course of hospitalization (but before confirmed VTE), so therapeutic AC could have followed clinical worsening.	Low Categories were clearly defined and documented in medical records	Unclear AC was defined based on actual treatment, not treatment assigned at baseline. 34.8% of patients did not adhere to prophylaxis (missed at least 2 days of AC prophylaxis), but not reported by level of AC.	VTE: High Mortality: Low VTE outcomes: No specific protocol for screening was in place; likely increased over time with awareness of coagulation. Those on higher AC may have been more likely to get VTE screening. In-hospital and 60-day mortality were clearly documented and unlikely to be misclassified by intervention status. Researchers conducted telephone follow up for 60-day mortality.	Low IPTW models adjust for important confounders (including time of admission and use of corticosteroids) and appear to be well balanced.
Voicu, 2021[17]	Unclear AC dosage was based on timing of admission, which would be a clear problem if the outcome were survival, but it's less clear whether the time trend also	Low Categories were clearly defined and documented in medical records	Unclear Deviations from interventions not reported; ECMO prevalence not balanced between intervention groups	Unclear All patients were systematically screened for DVT, but patients in intervention group had longer average time from ICU admission to 1st screening by 1 day	High No adjustments made for confounding

Author Year	a. Selection bias (High, Low, Unclear)	b. Bias in classification of interventions (High, Low, Unclear)	c. Bias due to departures from intended interventions (High, Low, Unclear)	d. Bias due to measurement of outcomes? (High, Low, Unclear)	e. Bias due to confounding? (High, Low, Unclear)
	affected incidence of DVT				
Yu, 2021[36]	Unclear 76% of patients in therapeutic AC group started within 72 hours of admission, but the median for pre-matched group was 3 days. Post matching medians are not. AC was treated as a time-varying factor, though it's unclear what this meant.	Low Categories were clearly defined and documented in medical records	Unclear Adherence is not reported. Co-interventions appear balanced between cohorts.	Low Mortality and bleeding events were clearly documented and unlikely to be misclassified by intervention status	Unclear PSM models adjust for important confounders (use of corticosteroids) and appear to be well balanced. It's unclear how well the time-varying treatment of exposure adjusted for confounding due to timing of admission.
Zermatten, 2020[42]	Low Included all patients meeting criteria during study period. Hospital had guidelines for all patients admitted to ICU and follow up started at admission.	Unclear Intervention groups defined by pre- post-guideline changes on Apr 7, but it's unclear how many patients were in each group.	Unclear No reporting of deviations from intervention protocol within each time frame. Co-interventions not reported by AC group.	High Screening for outcome likely increased over time with knowledge of clotting risks among COVID-19 patients, corresponding to changes over time in the guidance. Screening was based on clinical suspicion; no reported data on trends in screening/clinical suspicion over time	High Downward trend in VTE corresponded with overall trend in increased survival of chronically ill COVID-19 patients and earlier diagnosis and treatment of COVID-19 patients; overall improved care could confound the effect. No adjustment for confounding.

Abbreviations. AC=Anticoagulation, APTT=Activated partial thromboplastin time, CTPA=CT pulmonary angiogram, DVT=Deep vein thrombosis, ECMO=Extracorporeal membrane oxygenation, HR=Hazard ratio, ICU=Intensive care unit, IPTW= Inverse probability of treatment weighting, LMWH=Low molecular weight heparin, PSM=Propensity score matching, PE=Pulmonary embolism, SOFA= Sequential Organ Failure Assessment, VTE=Venous thromboembolism.

Quality Assessment of Observational Studies Based on the ROBINS-I Tool Continued (Columns f-j)

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
Al-Samkari, 2021[18]	Low Low level of missing data (1.4%) for early therapeutic AC vs no early AC comparison.	Low	Unclear	Unclear adherence to therapeutic AC	
Arachchillage, 2021[13]	Low All eligible patients included in analysis	Low	High	Lack of adjustment for confounding. Unclear time from admission of patients to screening for VTE (possible patients had VTE at start of study period)	
Atallah, 2020[37]	Low	Unclear Authors focus on a multivariate analysis that used maximum d-dimer over the course of ICU stay instead of ICU admission, but they make other results available in supplemental materials.	Unclear	Unclear risk of unaddressed confounding and adjustment for factors after start of intervention. Potential for differential assessment of outcome.	
Avruscio, 2020[38]	Low	Low All outcomes appear to be reported	Unclear	Unclear which outcome analyses were adjusted	
Benito, 2020[40]	Low Outcome data was available for all participants (built into inclusion criteria). No patients was excluded for missing intervention data	Low Single outcome, single intervention, no subgroup analyses	High	Administration of the intervention was ultimately left up to clinicians, despite guidelines recommending prophylaxis for all COVID-19 patients, and no attempt was made to account for potential risk of confounding by indication. Study only included	High risk that selection bias, confounding by indication, and lack of control biased the effect estimate--most likely toward the null value/overestimating relative risk of PE among patients treated with

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
				patients who had CTPA (and were therefore suspected of having PE/outcome).	LMWH compared to those not treated with LMWH.
Canoglu, 2020[20]	Unclear Unclear level and handling of missing data	Low	Unclear	Unclear balance of baseline characteristics. Unclear adherence to therapeutic AC.	
Copur, 2021[21]	Low No missing data.	Low	High	High risk of confounding by indication.	
Elmelhat, 2020[28]	Unclear Unclear level and handling of missing data	Low	High	No adjustment for potential confounders, which are likely present and influenced outcomes.	
Ferguson, 2020[22]	Low No evidence of exclusions for missing data or high % of covariates with missing data	Low	High	High risk of bis due to departures from initial intervention.	Bias due to departures from intended intervention would most likely bias results toward null value.
Gabara, 2021[14]	Low No missing data.	Low	High	High risk of confounding by indication. Although the conduct of the study is not suspect, groups were inherently different at baseline.	
Halaby, 2021[43]	Unclear Varying levels of missing data for covariates, missing data excluded from analysis	Low	Unclear	Unclear balance of baseline characteristics. Unclear adherence to AC dosages. Exclusion of missing data from analyses.	

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
Helms, 2021[30]	Unclear Unclear level and handling of missing data	Low	VTE: High Mortality and bleeding: Unclear	Unclear balance of baseline characteristics. Unclear adherence to AC dosages. Differential likelihood of screening for VTE is highly likely to have biased outcome measurement.	Increased likelihood of being screened for VTE in the therapeutic AC group would bias estimates toward the null, but lack of adjustment for changes in care over time (general increase in survival over time coincided with increase in prescription of therapeutic AC) would bias results away from null.
Hsu, 2020[7]	Unclear Patients excluded from multivariate analysis with no explanation (assume missing covariate data)	Low No indication of other outcomes not reported	Unclear	Clearest risk of bias is limitation of imaging/ screening for VTE events to cases where VTE is clinically suspected. Unclear risk of residual confounding.	Imaging limitations would be most likely to bias results toward the null value, resulting in an underestimate of the protective effect of higher intensity AC. Impact of limitations difficult to assess in other categories without more detailed reporting of methods.
Jimenez-Soto, 2020[8]	Unclear Unclear level and handling of missing data	Low	VTE: High Mortality: Unclear	Some differences in baseline characteristics at baseline but adjusted for. Unclear adherence to AC dosages.	
Jonmarker, 2020[3]	Low	Unclear All models are reported, but decisions/rationale for main models vs sensitivity analyses/appendix are unclear	Unclear	Lack of clarity on imaging criteria for VTE outcomes. No model presented where both time and glucocorticoids are included in the model.	Absence of glucocorticoids and time variable from main model likely resulted in an underestimate of true hazard ratios. Unclear if

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
					having both in model would result in null effect.
Kessler, 2020[44]	Low Outcome data available for all participants. Patients not excluded due to missing intervention data.	Low Single outcome, single intervention, no subgroup analyses	High	No control for confounding variables (*eg*, age and other anti-platelet medications with known bleeding side effects). As changes in intervention status were based on risk factors and symptoms that would be associated with additional medications known to cause bleeding, risk of confounding is high.	If present, bias due to confounding would likely bias the effect away from the null value, overestimating the association between increased AC dosages and bleeding events.
Kumar, 2021[9]	Low Some covariate values were missing; did not result in exclusion of participants from study (missing values were imputed).	Low	Unclear	The main limitation is that roughly half (129/251) of 1st in-hospital VTE events were diagnosed within 24 hours of admission, which means early warning signs of the outcome could have occurred at or before start of the intervention.	
Kuno, 2021[31]	Low Adjustments made for missing data are well-described.	Low	Unclear		
Lavinio, 2021[10]	Unclear Missing data is <10% for most variables, but ~50% for baseline fibrinogen levels. May be some residual confounding.	Low	Unclear	The wide range of dosages in the intervention group limits generalizability. Most patients received doses in the intermediate range, but some received therapeutic AC.	While not a threat to internal validity, the wide dosage range limits generalizability/usefulness of the study to centers considering intermediate dose AC but not therapeutic AC.

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
Lynn, 2021[34]	Low No patients missing AC or outcome data; missingness reported for covariates and is very low	Low	Unclear	Selection bias (unclear timing of AC initiation) and lack of adjustment for time trend or use of corticosteroids.	Unclear direction of bias--association between intervention and severity would result in underestimate of preventive impact, but connection to time trend and lack of adjustment for corticosteroid use would likely result in an overestimate.
Martinelli, 2021[4]	Unclear Patients with no endpoint (*ie*, still hospitalized) were censored, but the from the study flow it is unclear how many there were	Low	VTE: High Mortality and bleeding: Unclear	Selection bias--choice of intervention tied to both severity and time trends.	Unclear direction of bias--association between intervention and severity would result in underestimate of preventive impact, but connection to time trend and lack of adjustment for corticosteroid use would likely result in an overestimate.
Meizlish, 2021[5]	Unclear Missingness not reported; only 382 patients out of 1624 eligible are included in PSM cohort	Low	Unclear	Selection bias--choice of intervention tied to severity (d-dimer max) and not balanced by PSM. Departures from intended intervention-- group assigned based on max dose received. Incomplete control for confounding--model doesn't adjust for corticosteroid treatment.	Unclear direction of bias--use of max dose intervention classification and association between intervention and severity would result in underestimate of preventive impact, but lack of adjustment for corticosteroid use would likely result in an overestimate.

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
Moll, 2021[15]	Low All eligible patients appear to have outcome data and are included in analysis (if in the PSM cohort)	Low	High	By definition, not all patients considered for the PSM cohort had a chance to receive intermediate AC. Similarly, the use of historical control group makes it likely that the intervention group was more likely to be screened for VTE due to symptoms/clinical suspicion.	Confounding by indication and time trends would most like result in an underestimate of the protective effect of intermediate AC, but lack of control for steroid treatment could result in an overestimate.
Motta, 2020[24]	Low <10% excluded for missing data	Low	Unclear	Selection bias--PSM adjusting variables were time-varying and not restricted to baseline. Departures from intended intervention -- intervention group assigned based on max dose received. Incomplete control for confounding--model doesn't adjust for corticosteroid treatment.	Unclear direction of bias--use of max dose intervention classification and association between intervention and severity would result in underestimate of preventive impact, but lack of adjustment for corticosteroid use would likely result in an overestimate.
Paolisso, 2020[11]	Unclear Patients were excluded for lack of info on medications; unclear how many patients were excluded for this reason.	Low No - Focus of discussion and abstract may be selective, but all outcomes reported and no subgroup analyses	Unclear	Unclear risk of selection bias and confounding by indication, as the time between admission and start of intervention not reported. Unclear risk of bias due to exclusion of patients on full dose AC and lack of reporting on whether these patients were in one of included	Selection bias and confounding by indication likely not threats to main finding, as they would be most likely to bias results toward the null value. Lack of reporting on exclusion of patients on full-dose AC is more of a concern, as patients started on intermediate AC were on average sicker at baseline

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
				interventions at the start of follow up.	and may have been at higher risk of dose escalation. Would bias results away from null value.
Patel, 2020[26]	Low All eligible patients included in analysis	Low	Unclear	Unclear risk of selection bias and general lack of reporting	
Pesavento, 2020[16]	Low	Low Model selection method was clear and pre-specified	Unclear	Potential for residual confounding by indication	Bias would most likely result in an overestimate of the association between AC dosage and mortality or VTE
Pieralli, 2021[41]	Unclear All eligible patients appear to have outcome data and are included in univariate analysis, but it's unclear if all are included in multivariate analysis.	Low	High		
Stessel, 2020[12]	Low All eligible patients included in analysis	Low	High	Selection bias and differential screening protocols for DVT	Differential screening protocol likely resulted in overestimate of association between therapeutic AC and DVT but may have resulted in underestimate of association between therapeutic AC and mortality, as universal screening for DVT might have resulted in earlier treatment of

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
					complications. Initiation of intervention coincided with general time trends of improved survival, which would also result in an underestimate of the association between therapeutic AC and mortality.
Taccone, 2020[39]	Low Outcome data available for all patients. No exclusions for missing intervention or covariate data.	Unclear Little info provided on how multivariate model was built/why confounders were included or excluded	Unclear	Article + supplement are missing info on methods used to limit bias in many domains.	Bias due to exclusions after interventions started could bias the result away from the null value, resulting in an overestimate of the therapeutic benefits of high-dose prophylaxis.
Tacquard, 2021[6]	High 38.5% of patients missing AC status	Low	High	Selection bias--choice of intervention tied to both severity and time trends.	Unclear direction of bias--association between intervention and severity would result in underestimate of preventive impact, but connection to time trend and lack of adjustment for corticosteroid use would likely result in an overestimate.
Vaughn, 2021[19]	Low Only 4.8% of patients selected for full abstraction were excluded due to missing data.	Low	VTE: High Mortality: Unclear	Intervention assignment based on actual AC level received over the course of hospitalization makes it likely that, at least in some cases, therapeutic AC use followed clinical worsening. For VTE outcomes,	Limitations would most likely result in an overestimate in the risk of mortality and VTE due to therapeutic AC intervention.

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
				patients with clinical worsening (who were probably more likely to received therapeutic AC) likely received screening more often and therefore had a higher chance for confirmed VTE.	
Voicu, 2021[17]	Low All eligible patients included in analysis	Low	High	Lack of adjustment for confounding.	Most demographics and baseline factors appear balanced between groups, but APTT was higher in intervention cohort and ECMO more prevalent; these factors would likely result in an overestimate of the association between higher AC and DVT
Yu, 2021[36]	Low All patients have confirmed discharge or death outcome. Technically possible that patients could have been excluded for missing outcome but seems unlikely to have been a high proportion even if true.	Low	Unclear		
Zermatten, 2020[42]	Unclear Follow up stopped on May 3; may not have been long enough for outcomes to occur for	Low	High	Unclear distinction between intervention groups, lack of control for confounding trends over time and shorter follow up for	Lack of control for trends over time in improved patient care and outcomes for COVID-19 patients likely biased observed protective effect of

Author, Year	f. Bias due to missing data? (High, Low, Unclear)	g. Bias in the selection of reported results (High, Low, Unclear)	h. Overall bias (High, Low, Unclear)	i. What is the main limitation(s) of the study?	j. What are the implications of the limitations?
	patients treated under new guidelines.			patients on intermediate prophylaxis.	intermediate-dose AC on VTE outcomes away from the null value.

Abbreviations. AC=Anticoagulation, APTT=Activated partial thromboplastin time, CTPA=CT pulmonary angiogram, DVT=Deep vein thrombosis, ECMO=Extracorporeal membrane oxygenation, HR=Hazard ratio, ICU=Intensive care unit, IPTW= Inverse probability of treatment weighting, LMWH=Low molecular weight heparin, PSM=Propensity score matching, PE=Pulmonary embolism, SOFA= Sequential Organ Failure Assessment, VTE=Venous thromboembolism.

SUMMARY OF EVIDENCE

Summary of Evidence for Mortality Outcomes[a]

Intervention and comparator	Summary of Findings	SOE Grade	No. Studies, Study Design	Risk of Bias[b]	Directness	Consistency	Precision
Intermediate-dose anticoagulation vs standard thromboprophylaxis	Risk may be decreased	Low	2 RCT[1,2,45] 15 Cohorts[3-17]	Low or Some Concerns Unclear to High	Direct	Mostly consistent	Precise
Therapeutic-dose anticoagulation vs standard thromboprophylaxis	No difference	Low	6 RCTs[23,25,27,29,32,33] 18 Cohorts[3,7-9,14,18-22,24,26,28,30,31,34-36]	Unclear to High Low or Some Concerns	Direct	Mostly consistent	Precise

Notes.
[a] Reporting bias not detected.
[b] See Appendix C for details of quality assessment.
Abbreviations. NA=Not applicable; RCT=Randomized Control Trial.

Summary of Evidence for Thrombotic Event Outcomes[a]

Intervention and comparator	Summary of Findings	SOE Grade	No. Studies, Study Design	Risk of Bias[b]	Directness	Consistency	Precision
Intermediate-dose anticoagulation vs standard thromboprophylaxis	No difference	Low	2 RCTs[1,2,45] 18 Cohorts[3,4,6-10,12-15,17,37-42]	Low or Some concerns Unclear to High	Direct	Mostly consistent	Imprecise
Therapeutic-dose anticoagulation vs standard thromboprophylaxis	Risk may be decreased	Low	6 RCTs[23,25,27,29,32,33] 10 Cohorts[3,7-9,14,19,24,30,37,41]	Low to Some Concerns Unclear to High	Direct	Mostly consistent	Imprecise

Notes.
[a] Reporting bias not detected.
[b] See Appendix C for details of quality assessment.
Abbreviations. NA=Not applicable; RCT=Randomized Control Trial.

Summary of Evidence for Bleeding Event Outcomes[a]

Intervention and comparator	Summary of Findings	SOE Grade	Study Design No. Studies	Risk of Bias[b]	Directness	Consistency	Precision
Intermediate-dose anticoagulation vs standard thromboprophylaxis	Increased risk	Low[c]	2 RCTs[1,2,45] 17 Cohorts [3,4,7,8,10,11,13-17,37-39,41,43,44]	Low to Some Concerns Unclear to High	Direct	Consistent	Imprecise
Therapeutic-dose anticoagulation vs standard thromboprophylaxis	Increased risk	Low[c]	6 RCTs[23,25,27,29,32,33] 13 Cohorts[3,7,8,14,22,28,30,34,36,37,41,43,44]	Low or Some concerns Unclear to High	Direct	Consistent	Precise

Notes.
[a] Reporting bias not detected.
[b] See Appendix C for details of quality assessment.
[c] Low confidence in evidence specific to hospitalized adults with COVID-19.
Abbreviations. NA=Not applicable; RCT=Randomized Control Trial.

APPENDIX D: PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
Are the objectives, scope, and methods for this review clearly described?				
1	1	Yes	August	None
2	2	Yes	April/August	None
3	3	Yes	April/August	None
4	4	Yes	April/August	None
5	5	Yes	August	None
6	6	Yes	April	None
Is there any indication of bias in our synthesis of the evidence?				
7	1	No	August	None
8	2	No	April/August	None
9	3	No	April/August	None
10	4	No	April/August	None
11	5	No	August	None
12	6	No	April	None
Are there any published or unpublished studies that we may have overlooked?				
13	1	No	August	None
14	2	No	April	None
15	2	Yes - Recommend inclusion of the Multiplatform trial results published in NEJM on August 4, 2021. I realize this is not likely to change the overall results, but these recent studies have gotten a lot of attention and are somewhat controversial, in that a positive effect was seen only in the non-critically ill. References: DOI: 10.1056/NEJMoa2105911 and DOI: 10.1056/NEJMoa2103417	August	The final report includes these published studies (previously included as preprints).
16	3	Yes - See section below	April	The evidence brief has been updated to include searches through October 12, 2021.

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
17	3	No	April	None
18	4	Yes - - These studies were likely published after the ESP was completed but should be included: - 10.1001/jama.2021.4152 - 10.7326/M20-6739 - 10.1002/ajh.26102 - 10.1016/j.chest.2021.01.017	April	The evidence brief has been updated to include searches through October 12, 2021, which captured the recommended studies.
19	4	Yes - The recent NEJM studies on therapeutic anticoagulation among critically ill and non-critically ill patients with COVID	August	The final report includes the published studies (previously included as preprints).
20	5	No	August	None
21	6	Yes - More details on the ATTACC/RE-MAP-CAP/ATIV-4a mpRCT - covered only briefly in "ongoing studies" https://www.attacc.org/presentations	April	The final report includes 2 publications from the ATTACC/RE-MAP-CAP/ATIV-4a multi-platform RCT.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.				
22	1	Forest plots should include a synthesis restricted to RCT data. Meta-analysis of cohort studies including high risk of bias is potentially misleading. Also, as this is actively being discussed at NIH in light of ACTIV findings, references to current NIH guidelines may be outdated soon.	August	We revised forest plots to include syntheses restricted to RCT data. We also qualified our discussion of guidelines to indicate that we are discussing *current* guidelines.
23	1	This is a compete and clearly written report. They carefully review the nuances of the findings. I have only one concern/suggestion: given the high probability of bias in the cohort studies, as noted in their assessments, I suggest their Forest plots include a separate analysis of the RCTs alone. Although the authors mention some concerns, they clearly provide a qualitatively different view of the evidence. I suspect that doing so, and basing recommendations on the higher quality studies, may change the tone of conclusions around	August	Please see the response to comment #22.

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
		therapeutic dose anticoagulation. I recognize the limitations of basing strong recommendations on one subgroup analysis of the ACTIV trial, but I think that has to be given much more weight than the numerous cohort studies subject to strong confounding by indication.		
24	2	Nice summary of a rapidly evolving issue … recommend this be a "living review" with close monitoring of emerging evidence.	April	None
25	2	I believe the Rentsch paper may have been formally published in BMJ, so you should update the reference #16	April	The final report mentions the Rentsch study in the Discussion and we have updated the citation.
26	2	N/A	August	None
27	3	Thank you for the opportunity to review this ESP re: Antithrombotic therapies in COVID-19. The review is quite methodologically sound but, unfortunately, is now out of date -- this is one of the central challenges in performing reviews with COVID: the landscape changes on a monthly and sometimes even weekly basis. The two primary changes would involve the INNOVATION RCT which has at least a moderate strength of evidence showing the prophylactic intermediate dose anticoagulation is no better than standard dose and may be associated with harm. Second, the VA-data (BMJ) of early prophylactic dose anticoagulation, while observational, was performed about as well as an Obs study can do / almost a quasi trial, and showed that prophylaxis (vs. none) was associated w/ mortality reduction. So, the strength of evidence for 'standard vs. no' anticoagulation may now be higher than 'Low SoE' as is the case in the manuscript now.	April	The evidence brief has been updated to include searches through October 12, 2021. The reviewer is likely referring to the INSPIRATION trial which we included. Comments related to the VA-data (BMJ) study are no longer relevant given that the final version of the report was narrower in scope (with a focus on intermediate and therapeutic anticoagulation in the hospital setting) compared to the draft.
28	3	I fully recognize this would mean updating your search, revising the paper, and running the same	April	As above, the evidence brief has been updated to include searches through October 12, 2021. We

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
		risk again. Suggest that you scan clincaaltrials.gov for key current or upcoming trials to weigh your options on the timing of a review. With this background work done, it may also be possible to achieve a shorter interval between the end of the search and the final draft manuscript. Best of luck.		also included a table of ongoing trials in the Supplemental Materials.
29	3	THANK YOU for an undertaking a substantial revision in response to new data on intermediate vs. standard dose AC and for the evident challenges of working to synthesize evidence that changes nearly weekly.	August	None
30	3	As the authors are no doubt aware, the ATTACC/ACTIV-4a/REMAP-CAP results referenced here (18) in medrxiv have since been published in the N Engl J Med with the addition of "with heparin" now in the title (both the moderate severity and critical severity arms, in separate papers). The authors accurately portray the 28 day mortality data (not different) but don't provide readers the additional perspectives that may be useful: that the trial was stopped early due to meeting its primary endpoint of organ support free days at day 28 (which is a good thing -- therapeutic heparin was better than standard prophy); that major thrombosis or death was lower (but CI crossed 1); This largest RCT provides a basis to consider empiric therapeutic anticoagulation in moderately severely ill patients if the goal is to reduce organ support free days. The cautionary language around intermediate dose anticoagulation but absence of further explication around these findings for therapeutic dose anticoagulation feel at odds with one another.	August	The evidence brief now reflects the publication of ATTACC/ACTIV-4a/REMAP-CAP studies. We expanded our discussion of this trial, providing more detail on findings for the primary outcome of organ support-free days and attempting to put the trials findings in context.
31	3	Suggest adding a paragraph of text reflecting these aspects of this largest trial, recognizing	August	Please see the response to comment #30.

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
		that the statistics of an adaptive platform design are not necessarily intuitive, and that (a) trials stopped early for benefit can overestimate benefit and (b) because they studied a different endpoint, they lacked power to address the endpoint of 28d mortality in your review. The absolute benefit was 4% for their primary outcome, with an absolute harm of about 1% re: bleeding. Your ESP overall conclusion may be the same -- that it's not yet clear that the gains (about 1% lower 28 day mortality, not significantly different -- CIs cross 1) are worth the costs (1% higher major bleeding risk, also not sig diff, CIs cross 1). But communication of these results feels missing.		
32	3	On the table on page 25, the study by Sholzberg is described, w/ 465 participants in the two arms and demographic data; results are included in the subsequent tables and Forest plots. The reference, though (22), is to a Q&A with Dr. Sholzberg from mid-2020 that references the RAPID trial but offers no qualitative or quantitative data. It appears the RAPID manuscript was posted on medrxiv on July 9th, 2021, which would have been after your end date for the literature search. It has not yet been published in a peer reviewed journal that I can find. Is there another reference that was used in support of the RAPID study findings? The number of participants n=465 is the same as in the medrxiv posting -- seems like this is the paper you are referring to.	August	We have updated the citation for the trial by Sholzberg et al, which is now published.
33	3	May consider the following bottom line summary:	August	None
34	3	1. Prophylactic dose AC: High quality observational data (VA) suggest this is associated w/ lower mortality. Recommend	August	This comment no longer applies given our narrowed scope as discussed above.

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
		prophylaxis vs. no prophylaxis (i.e., COVID-19 in the hospital is enough -- don't use Padua)		
35	3	2. Intermediate dose AC: minor signal of benefit not enough to recommend it	August	Key Findings in the final report reflect this suggestion.
36	3	3. Therapeutic dose AC: while not enough to clearly recommend it, one large RCT showed increased number of organs support free days; d-dimer levels were not helpful in stratifying those who might benefit. Importantly, this was limited to MODERATE severity patients.	August	The comment is no longer relevant (results changed after search update and addition of meta-analysis).
37	4	Thank you for the opportunity to review this very well-conducted and well-written evidence brief. My comments are noted below, in order of importance.	April	None
38		1. The authors note in the 4th bullet of Key Findings as well as in other parts of the evidence brief (e.g., page 6, last paragraph) that they recommend the use of standard-dose thromboprophylaxis. However, my read of this brief seems to suggest that intermediate-dose thromboprophylaxis could also be considered reasonable, given the suggestion that it may have beneficial outcomes without clear evidence of harm. Now this opinion might change with the addition of the recent RCT (10.1001/jama.2021.4152), which demonstrated no benefit with intermediate-dose thromboprophylaxis. However, as the evidence brief is currently written, I think the authors should either clarify why intermediate-dose thromboprophylaxis is not a reasonable option or include it as a reasonable option.	April	The comment is no longer relevant (results changed after search update and addition of meta-analysis).
39		2. Table 3 – why does the Results Summary consider intermediate-dose prophylaxis to be associated with more bleeding events when two studies (totaling 805 patients) showed no	April	The comment is longer relevant (results changed after search update and addition of meta-analysis).

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
		difference but one study with 324 patients showed higher bleeding?		
40		3. Given the rise of preprint server use during the pandemic, should the authors differentiate studies that have undergone peer review from studies that have not? Along these lines, the Rentsch et al study was cited many times in the ESP so I think it is important to note that it was cited as a preprint but has now undergone peer review (10.1136/bmj.n311).	April	Please see the response to comment #25.
41		4. The authors should mention within the Methods the end date for the literature search. It appears to be November, based on the Summary and Discussion.	April	The new end search date (October 12, 2021) is included in the Methods section.
42		5. When considering therapeutic anticoagulation, clinicians sometimes have the option of using IV unfractionated heparin at two different therapeutic doses (i.e., at acute coronary syndrome dosing or at deep venous thrombosis/pulmonary embolism dosing). How would this be defined within the standard/intermediate/therapeutic scheme defined by the authors?	April	Most studies did not specify whether heparin protocols were specific for acute coronary syndrome dosing or DVT/PE. To improve transparency, we updated the study characteristics tables (Tables 2 and 3) to include medication dosing details as reported by study authors.
43		6. How did examined studies consider "presumed positive" COVID patients (i.e., patients who were clinically diagnosed with COVID but might not have had testing performed, which may have been more prevalent early in the pandemic)?	April	Because we included studies of patients with PCR-confirmed and clinically diagnosed COVID-19, we did not extract data on which studies included "presumed positive" patients. However, our impression is that most studies restricted inclusion to patients with laboratory-confirmed COVID-19.
44		7. On line 39 of page 5, the authors do not mention the strength of evidence for standard vs no thromboprophylaxis or for the continuation of chronic anticoagulation, though other comparisons do have strength of evidence.	April	This comment is no longer relevant due to the narrowed scope as discussed above.

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
45		8. In the Executive Summary Table: Results Overview on page 6 several abbreviations are included in the footnote, which do not appear to be in the Table.	April	The table and abbreviations list have been revised and updated for the final report.
46	4	I thank the authors for their tremendous efforts in updating this evidence synthesis. My only question/concern relates to the recent publications of two manuscripts in NEJM about the use of therapeutic anticoagulation among critically ill and non-critically ill patients with COVID. These studies seem important and very relevant to this evidence brief, and I worry about the publication of this brief without consideration of those studies - particularly in the face of the study of non-critically ill patients, which showed a mortality benefit. Otherwise, I think the authors have done a wonderful job and have nicely summarized the landscape. I have no additional comments.	August	The final report reflects the publication of ATTACC/ACTIV-4a/REMAP-CAP studies.
47	5	A few general comments 1) I thought the team did an excellent job in their synthesis of the data. Clearly there is an abundance of observational data and much less RCT data	August	None
48	5	2) I think the emphasis on mortality makes sense but not all trial data focus on this outcome. Further, it seems clear based on ACTIV data that there are differences in outcomes based on critically ill status and other than ACTIV there are no trial ata which makes ultimately determining recommendations difficult as this is the largest most definitive study to date.	August	Please see the response to comment #30.
49		3) It was interesting in the Intermediate vs. Standard therapy studies that nearly all the observational studies suggested a benefit and the one trial did not. Thus it makes it very hard to	August	The comment is no longer relevant (results changed after search update and addition of meta-analysis).

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
		make a recommendation based on observational data due to unmeasured confounding and having only one clinical trial makes it hard to make a recommendation, particularly when the numbers are relatively small (276 and 286 in the intervention and standard arms, respectively).		
50		4) If possible, in Figures for both comparisons (intermediate vs. prophylaxis and therapeutic vs prophylaxis-- having the number of deaths by study would be helpful. Many of these studies have small numbers and based on CI I suspect few events)	August	Thank you for the suggestion. We have made this change.
51		5) My only concern is with this report is the Lawler et al. NEJM Therapeutic Anticoagulation with Heparin in Non-critically ill patients COVID 19. This paper was reviewed for this report but was in the non-peer reviewed form. While the authors are correct that therapeutic AC did not significantly reduce mortality (if examined as its own outcome), when combined with other measures (i.e., survival without organ support there was a significant benefit)... bleeding was higher in the AC vs. prophylaxis group (1.9% vs 0.9%). Unlike the Bikdeli study mentioned above, this study had substantially more power (1171 and 1048 for Therapeutic and standard therapy, respectively). This study is one of the largest and most definitive to date. I know that other institutions, including Vanderbilt, are now advocating for therapeutic treatment for patients admitted with COVID-19 for non-critical illness unless contraindications. I am concerned that we may be missing some benefit for our veterans as a function of our approach (i.e., the focus on total mortality alone). I would be very curious to know what other reviewers thought with regards to this study.	August	Please see the response to comment #30.

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
52	6	Congratulations to the authors for embarking on a synthesis of quite possibly one of the most important questions for the acute management of COVID19, in perhaps one of the challenging, shaky evidence bases possible! Authors do a fantastic job pointing out all of the potential limitations of the observational studies reviewed, including selection bias, confirmation bias, measurement bias, lack of statistical power, confounding by indication, and confounding by accompanying/associated differences in treatment. Some comments below:	April	None
53		1. An additional limitation to the evidence that might be pointed out is the sheer dynamism of COVID19 - changes in patient populations, treatment approaches, indications for treatment make for a very unstable clinical landscape on which to generate stable evidence about treatments, especially from observational studies.	April	The limitations section now includes a discussion of the dynamic nature of evidence on COVID-19.
54		2. The critical review of the literature doesn't seem to be matched by some of the language in the key findings as well as the results. For example I was surprised by the statement "Evidence indicates" found in several parts of the results and the key findings, although the evidence was poor. Indicates could be misinterpreted as "evidence indicates treatment " in a superficial read by a clinician (me on my first skim).	April	We have attempted to improve clarity and consistency in our language.
55		3. One thing that might be emphasized more is the extremely wide confidence intervals demonstrated by most of the studies, and the very disparate RR's/OR's demonstrated. These further supports having low confidence in the evidence base here, as well as large variation in the study populations. (for example, Table 3 -	April	In the updated report, we provide more discussion of confidence intervals.

Comment #	Reviewer #	Comment	Version Reviewed (all 2021)	Author Responses
		OR of 0.26 [.06-.69] in the Atallah study examining intermediate prophylaxis, compared to the OR of 0.81 [.73-.90] in the VA study).		
56		4. If the observational studies reviewed were deemed insufficient to establish causal relationships, then perhaps causal language (Table 3 - "Therapeutic AC does not reduce mortality...") should be avoided to be clearer about the evidence strength.	April	We have attempted to improve clarity and consistency in our language.
57		5. Page 21: I believe that the VA study compared the outcomes among patients receiving any prophylactic dose of anticoagulation to patients who did not receive any dose of anticoagulation within 24 hours of admission (not "standard prophylaxis" as written). Standard prophylactic dosing could not be reliably defined due to an inability to accurately identify doses in VA data. this is important, since risk/benefit of the therapeutic doses would be accounted for/included in the association observed.	April	This comment is no longer relevant due to the narrowed scope as discussed above.
58		The interim results of the ATTACC/RE-MAP-CAP, and ACTIV-4a multiplatform RCT seems really critical to this review, albeit being a bit confusing to clinicians - but the authors only mention this in the "ongoing studies" section. It seems underemphasized given their importance to evidence here, and while interim, they are quite an improvement from the evidence from the observational studies that received review. Perhaps there could be more elaboration on these studies and their interim findings - and a more detailed explanation of the early termination which might provide a foundation for future ESP updates?	April	The updated evidence brief now includes 2 publications from the ATTACC/RE-MAP-CAP/ATIV-4a multi-platform RCT.

APPENDIX E: CURRENT GUIDELINES

Current Guidelines on Anticoagulation Dosing in Adults Hospitalized with COVID-19

Source	Relevant Recommendations	Date Published	Date Accessed
American College of Chest Physicians (CHEST)[47] Guideline Panel	• In acutely ill hospitalized patients with COVID-19, we recommend current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines. • In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.	9-01-2020	3-3-2022
American Society of Hematology (ASH)[48] Guideline Panel	• The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity anticoagulation in patients with COVID-19–related critical illness who do not have suspected or confirmed VTE (conditional recommendation based on low certainty in the evidence about effects). • *Draft statement open for public comment*: The ASH guideline panel suggests using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness 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). • Recommendations on therapeutic-intensity vs prophylactic intensity anticoagulation for critically-ill patients and intermediate-intensity vs prophylactic-intensity for acutely ill patients are forthcoming.	10-14-2021	3-3-2022
International Society of Thrombosis and Haemostasis[27] Expert Survey	• For VTE prophylaxis in non-ICU hospitalized COVID-19 patients, universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent. Intermediate-dose LMWH may also be considered (30% of respondents). • For VTE prophylaxis in sick ICU hospitalized COVID-19 patients, routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk. Intermediate-dose LMWH (50% of respondents) can also be considered in high risk patients. Patients with obesity as defined by actual body weight or BMI should be considered for a 50% increase in the dose of thromboprophylaxis. Treatment-dose heparin should not be considered for primary prevention until the results of randomized controlled trials are available.	5-27-2020	3-3-2022
National Institutes of Health[49] Guideline Panel	• For adults who require low-flow oxygen and do not require intensive care unit (ICU)-level care: the Panel recommends the use of a therapeutic dose of heparin for	2-24-2022	3-3-2022

Source	Relevant Recommendations	Date Published	Date Accessed
	patients with D-dimer levels above the upper limit of normal, who require low-flow oxygen, and who do not have an increased bleeding risk. • For adults who require ICU-level care, including those receiving high-flow oxygen: the Panel recommends using a prophylactic dose of heparin as VTE prophylaxis, unless a contraindication exists. The Panel recommends against the use of an intermediate dose (e.g., enoxaparin 1 mg/kg once daily) or a therapeutic dose of anticoagulation for VTE prophylaxis, except in a clinical trial.		
World Health Organization[50] Living Guidance	• 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 (conditional recommendation, very low certainty).	11-23-2021	3-3-2022

APPENDIX F: RESEARCH IN PROGRESS

Ongoing or Planned Trials of Anticoagulation in Adults Hospitalized with COVID-19

Study Title, NCT	Country, Sponsor	Population	Enrollment	Intervention(s)	Primary Outcome(s)	Status
Completed						
Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19 (IMPROVE) [51] NCT04367831	US, Columbia University	Adults with COVID-19 in the ICU and enrolled within 5 days of ICU admission	94 (actual)	Intermediate-dose anticoagulation compared to prophylactic-dose anticoagulation	Number of patients with clinically relevant venous or arterial thrombotic events in ICU	Anticipated primary completion date: NA, last updated posted 9/29/21
Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients (X-Covid 19) [52] NCT04366960	Italy, Niguarda Hospital	Adults hospitalized with laboratory-confirmed SARS-CoV-2 infection	189 (actual)	Enoxaparin 40mg twice daily compared to enoxaparin 40mg daily	DVT and PE	Anticipated primary completion date: NA, last updated posted 6/8/21
Recruiting						
Safety and Efficacy of Therapeutic Anticoagulation on Clinical Outcomes in Hospitalized Patients With COVID-19 [53] NCT04377997	US, Mass. General Hospital	Adults hospitalized with COVID-19 and D-dimer >1.5 g/mL without severe ARDS	300 (estimated)	Therapeutic anticoagulation compared to standard of care anticoagulation	Composite endpoint of death, cardiac arrest, symptomatic DVT, PE, arterial thromboembolism, MI, or hemodynamic shock; major bleeding	Anticipated primary completion date: 6/1/22, last update posted 2/22/22

Study Title, NCT	Country, Sponsor	Population	Enrollment	Intervention(s)	Primary Outcome(s)	Status
Effect of Prophylactic and Therapeutic Anticoagulants in Egyptian Patients With COVID-19 [54] NCT04736901	Egypt, Ain Shams University	Adults hospitalized with COVID-19 at high risk of clotting	90 (estimated)	Active comparators: Enoxaparin 40 mg/day, Enoxaparin 0.5 mg/kg every 12 hours, Rivaroxaban 20 mg once daily, Rivaroxaban 10 mg once daily, Apixaban 5 mg twice daily, Apixaban 2.5 mg twice daily	Change in clotting factors level; change in gas exchange over time; time to increase in oxygenation; duration of hospitalization	Anticipated primary completion date: 4/1/21, last update posted 2/4/21
Comparison of Two Different Doses of Bemiring in COVID-19 (BEMICOP) [55] NCT04604327	Spain, Clinica Universidad de Navarra, Universidad de Navarra	Adults hospitalized with COVID-19 and D-dimer >500ng/mL	164 (estimated)	Therapeutic-dose bemiparin (weight adjusted) compared to prophylactic bemiparin 3,500 IU/day for 10 days	Combined outcome including death, ICU admission, mechanical ventilatory support, progression to moderate or severe ARDS or arterial or venous thrombosis	Anticipated primary completion date: 5/31/21, last update posted 10/27/20
Standard vs High Prophylactic Doses or Anticoagulation in Patients with High Risk of Thrombosis Admitted with COVID-19 Pneumonia (PROTHROMCOVID) [56] NCT04730856	Spain, Hospital Universitario Infanta Leonor	Adults hospitalized with moderate COVID-19, at high-risk of clotting	600 (estimated)	Active comparators : Tinzaparin 4,500 IU/day, tinzaparin 100 IU/kg/day, and tinzaparin 175 IU/kg/day	VTE, mechanical ventilation, progression on the WHO scale; Overall survival at 30 days; Length of hospital and ICU stay	Anticipated primary completion date: 6/1/21, last update posted 6/4/21
Clinical Efficacy of Heparin and Tocilizumab in Patients with Severe COVID-19 Infection (HEPMAB) [57]	Brazil, University of Sao Paulo	Adults hospitalized with severe COVID-19 within 10 days of positive test	308 (estimated)	Therapeutic and prophylactic anticoagulation with and without tocilizumab	Clinical improvement in 30 days, defined as hospital discharge or reduction on	Anticipated primary completion date: 10/20/21, Last update posted 2/21/21

Study Title, NCT	Country, Sponsor	Population	Enrollment	Intervention(s)	Primary Outcome(s)	Status
NCT04600141					WHO progression scale	
Prevention of Arteriovenous Thrombotic Events in Critically-Ill COVID-19 Patients Trial (COVID-PACT) [58] NCT04409834	US, The TIMI Study Group	Adults in the ICU with acute SARS-CoV-2 infection	750 (estimated)	Full-dose or prophylactic-dose anticoagulation with and without antiplatelet therapy	Venous or arterial thrombotic events	Anticipated primary completion date: March 2022, last update posted 11/30/21
ANTIcoagulation in Severe COVID-19 Patients (ANTICOVID) [59] NCT04808882	France, Assistance Publique - Hôpitaux de Paris	Adults with severe COVID-19 pneumonia	353 (estimated)	Therapeutic anticoagulation compared to high-dose prophylactic anticoagulation compared to low-dose prophylactic anticoagulation	All-cause mortality at day 28; Number of days to clinical improvement assessed by WHO scale	Anticipated primary completion date: 2/1/22, last update posted 7/14/21
Steroids and Unfractionated Heparin in Critically Ill Patients with Pneumonia From COVID-19 Infection (STAUNCH-19) [60] NCT04528888	Italy, Massimo Girardis	Adults with hospitalized with COVID-19 requiring non-invasive or invasive mechanical ventilation with D-dimer >6 times the upper limit of normal	210 (estimated)	Therapeutic-dose UFH and methylprednisolone or standard prophylactic dose LMWH and methylprednisolone compared to standard prophylactic LMWH alone	All-cause mortality at day 28	Anticipated primary completion date: 7/30/21, last update posted 5/6/21
Enoxaparin at Prophylactic or Therapeutic Doses in COVID-19 (EMOS-COVID) [61] NCT04646655	Italy, ASST Fatebenefratelli Sacco	Adults age 18-80 with COVID-19 related pneumonia with moderate-severe respiratory failure (PaO2/FiO2<250) and/or markedly increased	300 (estimated)	Therapeutic-dose enoxaparin compared to prophylactic-dose enoxaparin	30-day mortality rate, progression of respiratory failure defined as duration of continuous positive pressure ventilation or ICU admission, or	Anticipated primary completion date: 12/31/22, last update posted 2/16/22

Study Title, NCT	Country, Sponsor	Population	Enrollment	Intervention(s)	Primary Outcome(s)	Status
		D-dimer level (>2000 ng/mL)			intubation; number of major bleeding episodes	
Not yet recruiting						
High Versus Low LMWH Dosages in Hospitalized Patients with Severe COVID-19 Pneumonia and Coagulopathy (COVID-19 HD)[62] NCT04408235	Italy, Azienda Ospedaliero-Universitaria di Modena	Adults age 18-80 with severe COVID-19 pneumonia and coagulopathy not requiring invasive mechanical ventilation	300 (estimated)	Enoxaparin 70 IU/kg twice daily compared to enoxaparin 4000 IU daily	Clinical worsening, defined as death, acute MI, symptomatic arterial or VTE, need invasive for non-invasive mechanical ventilation	Anticipated primary completion date: June 2021, last update posted 5/29/20

Abbreviations. ARDS= Acute respiratory distress syndrome; DVT=deep vein thrombosis; ICU=Intensive care unit; LMWH=low molecular weight heparin; MI=myocardial infarction; PE=pulmonary embolism; UFH=unfractionated heparin; WHO=World Health Organization.

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