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Question: DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity compared to Prophylactic intensity for Patients with COVID-19 related critical illness who do not have suspected or confirmed VTE

Setting: Inpatient

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity	Prophylactic intensity	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 7 days to 30 days)[ab]												
2[1,2,c]	randomised trials	not serious	not serious	serious[d]	very serious[e]	none	215/579 (37.1%)	18.9%[f]	OR 1.06 (0.84 to 1.35)[i]	9 more per 1,000 (from 25 fewer to 50 more)	⨁◯◯◯ Very low[l]	CRITICAL
								24.1%[g]		11 more per 1,000 (from 30 fewer to 59 more)		
								30.1%[h]		12 more per 1,000 (from 35 fewer to 67 more)		
Pulmonary embolism (follow-up: range 7 days to 30 days)[ak]												
2[1,2,c]	randomised trials	serious[l]	not serious	serious[d]	serious[m]	none[n]	15/575 (2.6%)	4.0%[f]	OR 0.33 (0.18 to 0.60)	26 fewer per 1,000 (from 33 fewer to 16 fewer)	⨁◯◯◯ Very low	CRITICAL
								8.0%[g]		52 fewer per 1,000 (from 65 fewer to 30 fewer)		
								15.3%[h]		97 fewer per 1,000 (from 122 fewer to 55 fewer)		
Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) (follow-up: range 7 days to 30 days)[ao]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity	Prophylactic intensity	Relative (95% CI)	Absolute (95% CI)		
2[1,2,c]	randomised trials	serious[l]	not serious	serious[d]	very serious[p]	none	11/575 (1.9%)	1.6%[f]	OR 0.86 (0.37 to 2.01)	2 fewer per 1,000 (from 10 fewer to 16 more)	⨁◯◯◯ Very low	CRITICAL
								4.0%[g]		5 fewer per 1,000 (from 25 fewer to 37 more)		
								9.4%[h]		12 fewer per 1,000 (from 57 fewer to 79 more)		

Major bleeding (follow-up: range 7 days to 30 days)[aq]

2[1,2,r]	randomised trials	not serious	not serious	serious[d]	very serious[s]	none	24/574 (4.2%)	1.7%[f]	OR 1.95 (0.75 to 5.09)[t]	16 more per 1,000 (from 4 fewer to 64 more)	⨁◯◯◯ Very low	CRITICAL
								2.4%[g]		22 more per 1,000 (from 6 fewer to 87 more)		
								3.3%[h]		29 more per 1,000 (from 8 fewer to 115 more)		

Multiple Organ Failure (follow-up: 30 days)[u]

1[1,v]	randomised trials	not serious	not serious	serious[w]	very serious[x]	none	6/43 (14.0%)	3.2%[f]	OR 2.68 (0.50 to 14.18)	49 more per 1,000 (from 16 fewer to 287 more)	⨁◯◯◯ Very low	CRITICAL
								7.9%[g]		108 more per 1,000 (from 38 fewer to 470 more)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity	Prophylactic intensity	Relative (95% CI)	Absolute (95% CI)		
								18.4%[h]		193 more per 1,000 (from 83 fewer to 578 more)		

Ischemic stroke (severe) (follow-up: range 7 days to 30 days; assessed with: any ischemic stroke)[y]

2[1,2,c]	randomised trials	serious[l]	not serious	serious[d]	very serious[z]	none	8/575 (1.4%)	0.6%[f]	OR 0.94 (0.36 to 2.45)	0 fewer per 1,000 (from 4 fewer to 9 more)	⨁◯◯◯ Very low	CRITICAL
								1.2%[aa]		1 fewer per 1,000 (from 8 fewer to 17 more)		
								2.3%		1 fewer per 1,000 (from 15 fewer to 32 more)		

Intracranial hemorrhage (follow-up: 30 days)[ab]

1[1,v]	randomised trials	not serious	not serious	serious[ac]	very serious[ad]	none	0/45 (0.0%)	0.0%[f]	not estimable	--	⨁◯◯◯ Very low[ae]	CRITICAL
								0.2%[g]				
								1.5%[h]				

Invasive mechanical ventilation (follow-up: 30 days)[af]

1[1,v]	randomised trials	not serious	not serious	serious[ag]	very serious[ah]	none	10/38 (26.3%)	8/35 (22.9%)	OR 1.21 (0.41 to 3.51)	35 more per 1,000 (from 120 fewer to 281 more)	⨁◯◯◯ Very low	CRITICAL

Limb amputation (follow-up: 30 days; assessed with: Major adverse limb event)[aai]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity	Prophylactic intensity	Relative (95% CI)	Absolute (95% CI)		
1[1,v]	randomised trials	not serious	not serious	serious[aj]	very serious[ak]	none	2/45 (4.4%)	0.0%[f]	OR 4.43 (0.21 to 95.06)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
								0.3%[g]		10 more per 1,000 (from 2 fewer to 219 more)		
								2.1%[h]		66 more per 1,000 (from 17 fewer to 650 more)		

ST-elevation myocardial infarction (follow-up: range 7 days to 30 days; assessed with: Any myocardial infarction)[aal]

2[1,2,c]	randomised trials	serious[i]	not serious	not serious[d]	very serious[z]	none	7/575 (1.2%)	0.0%[f]	OR 0.73 (0.28 to 1.94)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
								0.3%[g]		1 fewer per 1,000 (from 2 fewer to 3 more)		
								3.3%[h]		9 fewer per 1,000 (from 24 fewer to 29 more)		

Length of hospital admission

1[1]	randomised trials	not serious	not serious	serious[ac]	very serious[am]	none	45	38	-	MD 2 days more (0.44 more to 3.56 more)	⨁◯◯◯ Very low[i]	CRITICAL

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

a. Follow up durations from the observational studies informing the baseline risk

b. The decision thresholds for All-Cause Mortality were: 16 per 1,000 for Trivial/Small; 31 per 1,000 for Small/Moderate; 60 per 1,000 for Moderate/Large

c. mpRCT 2021 & unpublished data HEP-COVID 2021

d. In the control group, only 61% of all HEP-COVID patients (ICU group unknown) and 40% of REMAP-CAP/ACTIV-4a/ATTACC were on prophylactic-intensity anticoagulation. As higher intensities according to local practice were allowed in their protocols, not rated down for risk of bias but rated down one level for indirectness

e. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes moderate harm and small benefit; rated down 3 levels for very serious imprecision

f. Lower bound of the 95% CI for the pooled mean event rate among baseline risk studies

g. Pooled mean event rate among baseline risk studies

h. Upper bound of the 95% CI for the pooled mean event rate among baseline risk studies

i. Combining the adjusted OR from the mpRCT (aOR = 1.19; 95% credible interval 0.90-1.57 [reverse of reported aOR 0.84; 95% credible interval 0.64-1.11 for survival to discharge]) with the unadjusted OR from HEP-COVID resulted in a pooled OR that was comparable (OR = 1.16; 95% CI 0.89-1.50)

j. Very low certainty; rated down 3 levels for very serious imprecision

k. The decision thresholds for Pulmonary Embolism (Moderate severity) were: 27 per 1,000 for Trivial/Small; 53 per 1,000 for Small/Moderate; 103 per 1,000 for Moderate/Large

l. Patients and caregivers were unblinded during the trials, and it was unknown if there were important differences in how often diagnostic imaging tests were performed, and how often they were positive. Certainty was rated down for serious risk of bias

m. The 95% CI of the absolute effect estimate crosses one decision threshold and includes small benefit and moderate benefit; rated down 1 level for serious imprecision

n. Large effect upgrading does not apply because only one imprecise study was available

o. The decision thresholds for Proximal Deep Venous Thrombosis (Moderate severity) were: 37 per 1,000 for Trivial/Small; 73 per 1,000 for Small/Moderate; 142 per 1,000 for Moderate/Large

p. The 95% CI of the absolute effect estimate crosses one decision threshold and the effect estimate is based on few events; rated down 2 levels for very serious imprecision

q. The decision thresholds for Major Bleeding were: 23 per 1,000 for Trivial/Small; 46 per 1,000 for Small/Moderate; 89 per 1,000 for Moderate/Large

r. mpRCT 2021 & HEP-COVID 2021

s. The 95% CI of the absolute effect estimate crosses two decision thresholds and the effect estimate is based on few events; rated down 2 levels for very serious imprecision

t. Combining the adjusted OR from the mpRCT (aOR = 1.48; 95% credible interval 0.75-3.04) with the unadjusted OR from HEP-COVID resulted in a pooled OR that was comparable (OR = 1.90; 95% CI 0.58-6.22)

u. The decision thresholds for Multiple Organ Failure were: 18 per 1,000 for Trivial/Small; 36 per 1,000 for Small/Moderate; 70 per 1,000 for Moderate/Large

v. Unpublished data HEP-COVID 2021

w. Baseline risks based on renal replacement in the absence of data for multiple organ failure. In addition, only 61% of all HEP-COVID patients (ICU group unknown) were on prophylactic-intensity anticoagulation

x. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes small benefit and large harm; rated down 3 levels for very serious imprecision

y. The decision thresholds for Ischemic Stroke (severe) were: 18 per 1,000 for Trivial/Small; 36 per 1,000 for Small/Moderate; 69 per 1,000 for Moderate/Large

z. The effect estimate is based on few events; rated down 2 levels for very serious imprecision

aa. Pooled baseline risk from two studies

ab. The decision thresholds for Intracranial Hemorrhage were: 18 per 1,000 for Trivial/Small; 35 per 1,000 for Small/Moderate; 68 per 1,000 for Moderate/Large

ac. In the control group, only 61% of all HEP-COVID patients (ICU group unknown) were on prophylactic-intensity anticoagulation. As higher intensities according to local practice were allowed, not rated down for risk of bias but rated down one level for indirectness

ad. Unknown effect as no events were observed in the RCT; rated down 2 levels for very serious imprecision

ae. No relative effect estimate available

af. The decision thresholds for Invasive Mechanical Ventilation (long-term) were: 20 per 1,000 for Trivial/Small; 38 per 1,000 for Small/Moderate; 74 per 1,000 for Moderate/Large

ag. The baseline risk comes from one RCT, not observational studies, and may not represent risk in practice. In addition, only 61% of all HEP-COVID patients (ICU group unknown) in the control group were on prophylactic-intensity anticoagulation

ah. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes large harm and large benefit; rated down 3 levels for very serious imprecision

ai. The decision thresholds for Limb Amputation were: 21 per 1,000 for Trivial/Small; 41 per 1,000 for Small/Moderate; 80 per 1,000 for Moderate/Large

aj. The reported outcome was 'major adverse limb event'. In addition, only 61% of all HEP-COVID patients (ICU group unknown) in the control group were on prophylactic-intensity anticoagulation

ak. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes large harm and large benefit; rated down 3 levels for very serious imprecision

al. The decision thresholds for ST-elevation Myocardial Infarction were: 23 per 1,000 for Trivial/Small; 44 per 1,000 for Small/Moderate; 86 per 1,000 for Moderate/Large

am. Data from one RCT, small sample size of 83; rated down 3 levels for very serious imprecision

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