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Question: DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Intermediate-intensity compared to Prophylactic-intensity for Patients with COVID-19 related acute illness who do not have suspected or confirmed VTE (PICO 2a)

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 Intermediate-intensity	Prophylactic-intensity	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: range 5 days to 34 days)[a]												
2[1,2]	randomised trials	not serious[b]	not serious	not serious	extremely serious[c]	none	11/124 (8.9%)	6.7%[d]	**OR 2.21** (0.69 to 7.03)	**70 more per 1,000** (from 20 fewer to 268 more)	⨁◯◯◯ Very low	CRITICAL
								9.1%[e]		**90 more per 1,000** (from 26 fewer to 322 more)		
								12.3%[f]		**114 more per 1,000** (from 35 fewer to 373 more)		
Pulmonary embolism (follow-up: range 4 days to 34 days)[a]												
2[1,2]	randomised trials	serious[g]	not serious	not serious	extremely serious[c]	none	2/124 (1.6%)	1.8%[d]	**OR 0.42** (0.01 to 11.96)	**10 fewer per 1,000** (from 18 fewer to 162 more)	⨁◯◯◯ Very low	CRITICAL
								3.2%[e]		**18 fewer per 1,000** (from 32 fewer to 251 more)		
								5.6%[f]		**32 fewer per 1,000** (from 55 fewer to 359 more)		
Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) (follow-up: range 5 days to 34 days)[a]												

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 Intermediate-intensity	Prophylactic-intensity	Relative (95% CI)	Absolute (95% CI)		
2[1,2]	randomised trials						0/124 (0.0%)	0.5%[d]	not estimable		-	CRITICAL
								0.9%[e]				
								1.5%[f]				

Major bleeding (follow-up: range 5 days to 90 days)[a]

2[1,2]	randomised trials	not serious[b]	not serious	not serious	extremely serious[h]	none	1/124 (0.8%)	0.6%[d]	**OR 1.01** (0.06 to 16.41)	**0 fewer per 1,000** (from 6 fewer to 84 more)	⨁◯◯◯ Very low	CRITICAL
								1.1%[e]		**0 fewer per 1,000** (from 10 fewer to 143 more)		
								2.1%[f]		**0 fewer per 1,000** (from 20 fewer to 239 more)		

Multiple organ failure (follow-up: mean 30 days)

1[2]	randomised trials	not serious	not serious	not serious	extremely serious[h]	none	3/91 (3.3%)	2/91 (2.2%)	**OR 1.53** (0.25 to 9.40)	**11 more per 1,000** (from 16 fewer to 152 more)	⨁◯◯◯ Very low	CRITICAL

Ischemic stroke (severe) (follow-up: range 5 days to 30 days)

2[1,2]	randomised trials	serious[g]	not serious	not serious	extremely serious[h]	none	2/124 (1.6%)	0.2%[d]	**OR 1.37** (0.09 to 20.07)	**1 more per 1,000** (from 2 fewer to 37 more)	⨁◯◯◯ Very low	CRITICAL
								0.4%[e]		**1 more per 1,000** (from 4 fewer to 71 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 Intermediate-intensity	Prophylactic-intensity	Relative (95% CI)	Absolute (95% CI)		
								1.0%[f]		**4 more per 1,000** (from 9 fewer to 159 more)		

Intracranial hemorrhage (follow-up: range 5 days to 90 days)

2[1,2]	randomised trials						0/124 (0.0%)	0.0%	not estimable		-	CRITICAL
								0.0%				
								1.1%				

Invasive ventilation (follow-up: range 28 days to 30 days)[a]

2[1,2]	randomised trials	not serious	not serious	not serious	extremely serious[i]	none	10/124 (8.1%)	4.5%[d]	**OR 0.99** (0.39 to 2.50)	**0 fewer per 1,000** (from 27 fewer to 60 more)	⨁◯◯◯ Very low	CRITICAL
								7.4%[e]		**1 fewer per 1,000** (from 44 fewer to 93 more)		
								11.9%[f]		**1 fewer per 1,000** (from 69 fewer to 133 more)		

Limb amputation (follow-up: range 10 days to 30 days; assessed with: Major adverse limb event)

1[2]	randomised trials						0/91 (0.0%)	0.0%	not estimable		-	CRITICAL
								0.1%				
								1.0%				

ICU hospitalization (follow-up: range 3 days to 30 days)

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 Intermediate-intensity	Prophylactic-intensity	Relative (95% CI)	Absolute (95% CI)		
1[2]	randomised trials	not serious	not serious	not serious	extremely serious[i]	none	6/91 (6.6%)	6.1%	**OR 1.01** (0.31 to 3.26)	**1 more per 1,000** (from 41 fewer to 114 more)	⨁◯◯◯ Very low	CRITICAL
								9.4%		**1 more per 1,000** (from 63 fewer to 159 more)		
								14.1%		**1 more per 1,000** (from 93 fewer to 208 more)		

ST-elevation myocardial infarction (follow-up: range 5 days to 30 days)

2[1,2]	randomised trials	not serious	not serious	not serious	extremely serious[i]	none	0/124 (0.0%)	0.2%[d]	**OR 0.32** (0.03 to 3.16)	**1 fewer per 1,000** (from 2 fewer to 4 more)	⨁◯◯◯ Very low	CRITICAL
								0.6%[e]		**4 fewer per 1,000** (from 6 fewer to 13 more)		
								1.7%[f]		**11 fewer per 1,000** (from 16 fewer to 35 more)		

CI: confidence interval; **OR:** odds ratio

Explanations

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

b. Both trials were open-label, and one trial had unblinded outcome assessors, but unlikely to have affected this outcome

c. The 95% CI of the absolute effect includes both large harm and small benefit

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

e. Pooled mean event rate among baseline risk studies

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

g. Both trials were open-label, and one trial had unblinded outcome assessors

h. The 95% CI of the absolute effect includes both trivial benefit and large harm

i. The 95% CI of the absolute effect includes both moderate benefit and large harm

j. The pooled effect estimate is based on a total of only two events

References

1.Perepu, U. S., Chambers, I., Wahab, A., Ten Eyck, P., Wu, C., Dayal, S., Sutamtewagul, G., Bailey, S. R., Rosenstein, L. J., Lentz, S. R.. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial. J Thromb Haemost; Sep 2021.

2.Morici, N., Podda, G., Birocchi, S., Bonacchini, L., Merli, M., Trezzi, M., Massaini, G., Agostinis, M., Carioti, G., Saverio Serino, F., Gazzaniga, G., Barberis, D., Antolini, L., Grazia Valsecchi, M., Cattaneo, M.. Enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients: The X-COVID-19 Randomized Trial. Eur J Clin Invest; May 2022.