Author(s):

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

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)		
All-cause mortality (follow-up: range 5 days to 50 days)[ab]												
5[1,2,3,4,5]	randomised trials	not serious[c]	serious[d]	not serious	very serious[e]	none	136/1825 (7.5%)	7.0%[f,g]	OR 0.78 (0.43 to 1.40)[j,k]	15 fewer per 1,000 (from 39 fewer to 25 more)[j]	⨁◯◯◯ Very low	CRITICAL
								9.6%[g,h]		20 fewer per 1,000 (from 52 fewer to 33 more)[m,n]		
								13.0%[g,i]		26 fewer per 1,000 (from 70 fewer to 43 more)[o]		
Pulmonary embolism - Moderate severity (follow-up: range 4 days to 34 days; assessed with: Pulmonary embolism)[ap]												
5[1,2,3,4,5]	randomised trials	serious[q]	not serious	not serious	not serious	none	20/1834 (1.1%)	1.6%[f,r]	OR 0.42 (0.25 to 0.71)	9 fewer per 1,000 (from 12 fewer to 5 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
								3.0%[h,r]		17 fewer per 1,000 (from 22 fewer to 9 fewer)		
								5.5%[i,r]		31 fewer per 1,000 (from 41 fewer to 15 fewer)		
Deep Venous Thrombosis of the upper leg - Moderate severity (follow-up: range 4 days to 34 days; assessed with: Deep venous thrombosis)[as]												

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)		
5[1,2,3,4,5]	randomised trials	serious[q]	not serious	not serious	serious[t]	none	14/1834 (0.8%)	0.5%[f,u]	OR 0.56 (0.22 to 1.41)	2 fewer per 1,000 (from 4 fewer to 2 more)	⨁⨁◯◯ Low	CRITICAL
								0.9%[h,u]		4 fewer per 1,000 (from 7 fewer to 4 more)		
								1.5%[j,u]		7 fewer per 1,000 (from 12 fewer to 6 more)		

Major bleeding (follow-up: range 5 days to 30 days)[av]

5[1,2,3,4,5]	randomised trials	not serious[w]	not serious	not serious	serious[x]	none	36/1834 (2.0%)	0.6%[f,y]	OR 1.79 (1.00 to 3.21)[z]	5 more per 1,000 (from 0 fewer to 13 more)	⨁⨁⨁◯ Moderate	CRITICAL
								1.2%[h,y]		9 more per 1,000 (from 0 fewer to 26 more)		
								2.3%[j,y]		17 more per 1,000 (from 0 fewer to 47 more)		

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

3[2,3,4]	randomised trials	serious[ab]	not serious	serious[ac]	very serious[ad]	none	5/344 (1.5%)	1.7%[ae,f]	OR 0.46 (0.03 to 6.59)	9 fewer per 1,000 (from 16 fewer to 85 more)	⨁◯◯◯ Very low	CRITICAL
								5.0%[ae,h]		26 fewer per 1,000 (from 48 fewer to 208 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)		
								13.6%[ae,i]		68 fewer per 1,000 (from 131 fewer to 373 more)		

Ischemic stroke - Severe (follow-up: range 5 days to 30 days; assessed with: Ischemic stroke)[aaf]

5[1,2,3,4,5]	randomised trials	not serious[c]	not serious	not serious	very serious[ag]	none	3/1834 (0.2%)	0.1%[ah,f]	OR 0.92 (0.19 to 4.48)	0 fewer per 1,000 (from 1 fewer to 3 more)	⨁◯◯◯ Very low	CRITICAL
								0.4%[ah,h]		0 fewer per 1,000 (from 3 fewer to 14 more)		
								1.1%[ah,i]		1 fewer per 1,000 (from 9 fewer to 36 more)		

Intracranial hemorrhage (follow-up: range 5 days to 30 days)[aai]

5[1,2,3,4,5]	randomised trials	not serious[c]	not serious	not serious	very serious[aj]	none	1/1834 (0.1%)	0.0%[ak,f]	OR 2.95 (0.12 to 72.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
								0.0%[ak,h]		0 fewer per 1,000 (from 0 fewer to 0 fewer)		
								1.0%[ak,i]		19 more per 1,000 (from 9 fewer to 414 more)		

Invasive mechanical ventilation - Long-term (follow-up: range 7 days to 30 days; assessed with: Invasive mechanical ventilation)[aal]

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)		
3[2,3,4]	randomised trials	serious[am]	not serious	not serious	serious[e]	none	22/344 (6.4%)	2.3%[an,f]	OR 0.69 (0.39 to 1.22)	7 fewer per 1,000 (from 14 fewer to 5 more)	⨁⨁◯◯ Low	CRITICAL
								5.3%[an,h]		16 fewer per 1,000 (from 32 fewer to 11 more)		
								11.8%[an,i]		33 fewer per 1,000 (from 68 fewer to 22 more)		

Limb amputation (follow-up: range 28 days to 30 days; assessed with: Major adverse limb event)[aoap]

4[1,2,3,4]	randomised trials	not serious	not serious	serious[aq]	very serious[ar]	none	0/654 (0.0%)	0.0%[as]	OR 0.33 (0.01 to 8.03)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
								0.2%		1 fewer per 1,000 (from 2 fewer to 14 more)		
								1.2%		8 fewer per 1,000 (from 12 fewer to 77 more)		

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

3[2,3,4]	randomised trials	serious[am]	not serious	not serious	serious[e]	none	44/344 (12.8%)	4.5%[au,f]	OR 0.80 (0.52 to 1.23)	9 fewer per 1,000 (from 21 fewer to 10 more)	⨁⨁◯◯ Low	CRITICAL
								8.3%[au,h]		15 fewer per 1,000 (from 38 fewer to 17 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)		
								14.6%[au,i]		26 fewer per 1,000 (from 64 fewer to 28 more)		
ST-elevation myocardial infarction (follow-up: range 5 days to 30 days; assessed with: Myocardial infarction)[aav]												
5[1,2,3,4,5]	randomised trials	not serious	not serious	not serious	very serious[aw]	none	2/1834 (0.1%)	0.1%[ax,f]	OR 0.65 (0.14 to 2.97)	0 fewer per 1,000 (from 1 fewer to 2 more)	⨁◯◯◯ Very low	CRITICAL
								0.4%[ax,h]		1 fewer per 1,000 (from 3 fewer to 8 more)		
								1.7%[ax,i]		6 fewer per 1,000 (from 15 fewer to 32 more)		

CI: confidence interval; 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. Although the ATTACC/ACTIV-4/REMAP-CAP trial used response-adaptive randomization that led to some loss in prognostic balance between the groups, the panel decided not to rate down the certainty for risk of bias as the pooled absolute effect estimate was similar when using the platform trial's adjusted OR, and the evidence was already rated down for serious inconsistency and very serious imprecision. The lack of blinding was not thought to have a large impact on risk of bias for the outcome of mortality

d. Heterogeneity in meta-analysis: I squared value 67%, Chi-square p-value for heterogeneity 0.02; substantially different point estimates and non-overlapping 95% CI's

e. The 95% CI of the absolute effect crosses at least one decision threshold and includes both trivial harm and small benefit

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

g. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 17 observational studies

h. Pooled mean event rate among baseline risk studies

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

j. Combining the adjusted OR from the ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial (aOR = 0.83; 95% credible interval 0.59-1.15) with the unadjusted OR's from the other trials resulted in a pooled OR that was comparable (OR = 0.77; 95% CI 0.44-1.35)

k. Removing the ACTION trial in sensitivity analysis, as the only trial testing a direct oral anticoagulant, the pooled OR was 0.60 (95% CI: 0.29-1.22)

l. Using the OR for UFH/LMWH trials only in sensitivity analysis (excluding ACTION), the effect as 27 fewer (from 49 fewer to 14 more)

m. Using the OR for UFH/LMWH trials only in sensitivity analysis (excluding ACTION), the effect as 27 fewer (from 49 fewer to 14 more)

n. Using the OR for UFH/LMWH trials only in sensitivity analysis (excluding ACTION), the effect as 36 fewer (from 66 fewer to 19 more)

o. Using the OR for UFH/LMWH trials only in sensitivity analysis (excluding ACTION), the effect as 48 fewer (from 88 fewer to 24 more)

p. 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

q. 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

r. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 9 observational studies

s. 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

t. The low baseline risk makes it unlikely that a clinically meaningful absolute risk reduction can be achieved. However, the certainty was rated down by one level for serious imprecision due to the combination of the wide 95% CI of the OR, not meeting the optimal information size, and imprecision in the baseline risk estimates

u. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 9 observational studies

v. 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

w. Although the ATTACC/ACTIV-4/REMAP-CAP trial used response-adaptive randomization that led to some loss in prognostic balance between the groups, the panel decided not to rate down the certainty for risk of bias as the pooled absolute effect estimate was already rated down for very serious imprecision

x. The 95% CI of the absolute effect crosses one decision threshold and includes both small harm and no effect

y. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 9 observational studies

z. Combining the adjusted OR from the ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial (aOR = 1.80; 95% credible interval 0.90-3.74) with the unadjusted OR's from the other trials resulted in a pooled OR that was comparable (OR = 1.62; 95% CI 0.94-2.81)

aa. 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

ab. Outcome data missing for two large RCTs, and one data from one trial represent multi-organ failure as primary cause of death

ac. Outcome in trial was multi-system organ failure as cause of death

ad. The 95% CI of the absolute effect crosses at least three decision thresholds and includes both large harm and moderate benefit; relative effect estimate based on a total of 14 events from 3 trials

ae. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from one RCT and 2 observational studies

af. 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

ag. The low baseline risk makes it unlikely that a clinically meaningful absolute risk reduction can be achieved. However, the certainty was rated down by three levels for very serious (extremely serious) imprecision due to the combination of the wide 95% CI of the OR, clearly not meeting the optimal information size, (6 events) and imprecision in the baseline risk estimates

ah. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 3 observational studies

ai. 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

aj. The certainty was rated down by three levels for very serious (extremely serious) imprecision due to the combination of the very wide 95% CI of the OR, clearly not meeting the optimal information size (1 event), and imprecision in the baseline risk estimates

ak. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 2 observational studies

al. 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

am. Outcome data missing for two large RCTs

an. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 6 observational studies

ao. Follow-up duration for Lopes 2021, from which the baseline risk and effect estimate were used

ap. 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

aq. Two trials reported on 'major adverse limb events', which was considered a surrogate outcome for limb amputation.

ar. The low baseline risk makes it unlikely that a clinically meaningful absolute risk reduction can be achieved. However, the certainty was rated down by two levels for very serious imprecision due to the combination of the wide 95% CI of the OR, clearly not meeting the optimal information size, (1 event) and imprecision in the baseline risk estimates

as. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs

at. The decision thresholds for ICU Admission were: 25 per 1,000 for Trivial/Small; 50 per 1,000 for Small/Moderate; 96 per 1,000 for Moderate/Large

au. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 7 observational studies

av. 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

aw. The low baseline risk makes it unlikely that a clinically meaningful absolute risk reduction can be achieved. However, the certainty was rated down by three levels for very serious (extremely serious) imprecision due to the combination of the wide 95% CI of the OR, clearly not meeting the optimal information size, (6 events) and imprecision in the baseline risk estimates

ax. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 2 observational studies

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