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)[a]												
3 [1,2,3]	randomised trials	not serious [b]	serious [c]	not serious	very serious [d]	none	125/1709 (7.3%)	7.2% [e,f]	OR 0.79 (0.37 to 1.68) [i,j]	14 fewer per 1,000 (from 44 fewer to 43 more)	⨁◯◯◯ VERY LOW	CRITICAL
								9.9% [f,g]		19 fewer per 1,000 (from 60 fewer to 57 more)		
								13.4% [f,h]		25 fewer per 1,000 (from 80 fewer to 72 more)		
Pulmonary embolism (follow up: range 4 days to 34 days)[a]												
3 [1,2,3]	randomised trials	serious [k]	not serious	not serious	serious [l]	none	18/1718 (1.0%)	1.7% [e,m]	OR 0.46 (0.26 to 0.81) [n]	9 fewer per 1,000 (from 13 fewer to 3 fewer)	⨁⨁◯◯ LOW	CRITICAL
								3.0% [g,m]		16 fewer per 1,000 (from 22 fewer to 6 fewer)		
								5.3% [h,m]		28 fewer per 1,000 (from 39 fewer to 10 fewer)		

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)		
Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) (follow up: range 5 days to 34 days)[a]												
3 [1,2,3]	randomised trials	serious [k]	not serious	not serious	serious [o]	none	12/1718 (0.7%)	0.5% [e,p]	OR 0.81 (0.37 to 1.75) [q]	1 fewer per 1,000 (from 3 fewer to 4 more)	⨁⨁◯◯ LOW	CRITICAL
								0.9% [g,p]		2 fewer per 1,000 (from 6 fewer to 7 more)		
								1.5% [h,p]		3 fewer per 1,000 (from 9 fewer to 11 more)		
Venous thromboembolism (follow up: range 5 days to 34 days)[a]												
2 [1,3]	randomised trials	serious [k]	not serious	not serious	serious [o]	none	13/538 (2.4%)	2.2% [e,r]	OR 0.51 (0.26 to 1.02) [s]	11 fewer per 1,000 (from 16 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
								3.6% [g,r]		17 fewer per 1,000 (from 26 fewer to 1 more)		
								5.9% [h,r]		28 fewer per 1,000 (from 43 fewer to 1 more)		
Major bleeding (follow up: range 5 days to 30 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 Therapeutic-intensity	Prophylactic-intensity	Relative (95% CI)	Absolute (95% CI)		
3 [1,2,3]	randomised trials	not serious [t]	not serious	not serious	very serious [u]	none	34/1718 (2.0%)	0.7% [e,v]	OR 1.80 (0.87 to 3.75) [w,x]	6 more per 1,000 (from 1 fewer to 19 more)	⨁⨁◯◯ LOW	CRITICAL
								1.3% [g,v]		10 more per 1,000 (from 2 fewer to 34 more)		
								2.3% [h,v]		18 more per 1,000 (from 3 fewer to 58 more)		

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

1 [3]	randomised trials	not serious	not serious	serious [y]	very serious [z]	none	0/228 (0.0%)	5.1% [aa,e]	OR 0.09 (0.01 to 1.68)	46 fewer per 1,000 (from 50 fewer to 32 more)	⨁◯◯◯ VERY LOW	CRITICAL
								7.2% [aa,g]		65 fewer per 1,000 (from 71 fewer to 43 more)		
								10.2% [aa,h]		92 fewer per 1,000 (from 101 fewer to 58 more)		

Ischemic stroke (severe) (follow up: range 5 days to 30 days; assessed with: any stroke)[a]

3 [1,2,3]	randomised trials	not serious [b]	not serious	not serious	very serious [ab]	none	2/1718 (0.1%)	0.1% [ac,e]	OR 0.88 (0.13 to 5.99) [ad]	0 fewer per 1,000 (from 1 fewer to 5 more)	⨁⨁◯◯ LOW	CRITICAL

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)		
								0.4% [ac,g]		0 fewer per 1,000 (from 3 fewer to 19 more)		
								1.1% [ac,h]		1 fewer per 1,000 (from 10 fewer to 51 more)		

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

3 [1,2,3]	randomised trials	not serious [b]	not serious	not serious	very serious [ab]	none	1/1718 (0.1%)	0.0% [ae,e]	OR 2.95 (0.12 to 72.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
								0.0% [ae,g]		0 fewer per 1,000 (from 0 fewer to 0 fewer)		
								1.0% [ae,h]		19 more per 1,000 (from 9 fewer to 414 more)		

Invasive mechanical ventilation (follow up: range 7 days to 30 days)[a]

1 [3]	randomised trials	not serious	not serious	not serious	very serious [d]	none	11/228 (4.8%)	1.8% [af,e]	OR 0.70 (0.32 to 1.54) [ag]	5 fewer per 1,000 (from 12 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL
								4.8% [af,g]		14 fewer per 1,000 (from 32 fewer to 24 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)		
								12.4% [af,h]		34 fewer per 1,000 (from 81 fewer to 55 more)		

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

1 [1]	randomised trials	not serious	not serious	serious [ai]	very serious [ab]	none	0/310 (0.0%)	1/304 (0.3%)	OR 0.33 (0.01 to 8.03)	2 fewer per 1,000 (from 3 fewer to 23 more)	⨁◯◯◯ VERY LOW	CRITICAL

ICU hospitalization (follow up: range 3 days to 28 days)[a]

1 [3]	randomised trials	not serious	not serious	not serious	very serious [d]	none	33/228 (14.5%)	3.9% [aj,e]	OR 0.79 (0.48 to 1.29)	8 fewer per 1,000 (from 20 fewer to 11 more)	⨁⨁◯◯ LOW	CRITICAL
								7.8% [aj,g]		15 fewer per 1,000 (from 39 fewer to 20 more)		
								14.9% [aj,h]		27 fewer per 1,000 (from 71 fewer to 35 more)		

ST-elevation myocardial infarction (follow up: range 5 days to 30 days; assessed with: Any myocardial infarction)[a]

3 [1,2,3]	randomised trials	not serious	not serious	not serious	very serious [ak]	none	2/1718 (0.1%)	0.1% [al,e]	OR 0.96 (0.17 to 5.54) [am]	0 fewer per 1,000 (from 1 fewer to 5 more)	⨁⨁◯◯ LOW	CRITICAL

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)		
								0.5% [a,l,g]		0 fewer per 1,000 (from 4 fewer to 22 more)		
								1.8% [a,l,h]		1 fewer per 1,000 (from 15 fewer to 74 more)		

CI: Confidence interval; OR: Odds ratio

Explanations

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

b. 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 serious inconsistency and very serious imprecision

c. Heterogeneity in meta-analysis: I squared value 80%, Chi-square p-value for heterogeneity 0.006; substantially different point estimates and non-overlapping 95% CI's

d. The 95% CI of the absolute effect includes both considerable harm and considerable benefit

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

f. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Al-Samkari 2020, Arachchillage 2021, Artifoni 2020, Boari 2020, Campochiaro 2020, Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Fortini 2020, Ierardi 2021, Kevorkian 2021, Martinelli 2021, Paolisso 2020, Pesavento 2020, Piazza 2020, Russo 2020, Santoliquido 2020, Soni 2020

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 ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial (aOR = 0.83; 95% credible interval 0.59-1.15) with the unadjusted OR's from Lopes 2021 (OR = 1.55; 95% CI 0.89-2.69) and Sholzberg 2021 (OR = 0.22; 95% CI 0.07-0.65) resulted in a pooled OR that was comparable (OR = 0.76; 95% CI 0.35-1.65)

j. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.80 (95% CI: 0.46-1.36)

k. 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

l. The 95% CI of the absolute effect includes both considerable benefit and negligible benefit

m. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Arachchillage 2021, Artifoni 2020, Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Louhaichi 2020, Middeldorp 2020, Moll 2020, Pancani 2020, Pesavento 2020, Piazza 2020, Russo 2020

n. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.44 (95% CI: 0.26-0.73)

o. The pooled analysis included few events, and the 95% CI of the absolute effect included both benefit and harm

p. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Arachchillage 2021,Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Moll 2020, Pancani 2020, Pesavento 2020, Piazza 2020, Russo 2020

q. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.54 (95% CI: 0.30-0.98)

r. Baseline risks were calculated using the control group risks from the two RCTs and the following observational studies: Al-Samkari 2020, Arachchillage 2021,Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Mei 2020, Moll 2020, Pesavento 2020, Russo 2020

s. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.51 (95% CI: 0.26-1.02)

t. 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

u. The 95% CI of the absolute effect includes both considerable harm and negligible benefit

v. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Al-Samkari 2020, Arachchillage 2021, Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Fujiwara 2021, Moll 2020, Pancani 2020, Paolisso 2020, Pesavento 2020, Russo 2020

w. 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 Lopes 2021 (OR = 2.50; 95% CI 0.78-8.04) and Sholzberg 2021 (OR = 0.52; 95% CI 0.09-2.84) resulted in a comparable pooled effect (OR = 1.65; 95% CI 0.87-3.16)

x. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 1.79 (95% CI: 1.00-3.21)

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

z. The 95% CI of the absolute effect includes both considerable harm and considerable benefit; effect estimate based on a total of 5 events from 1 trial

aa. Baseline risks were calculated using the control group risks from the RCT and the following observational studies: Arachchillage 2021, Piazza 2020

ab. Baseline risk and effect estimate based on a total of 1 event

ac. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Arachchillage 2021, Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Piazza 2020

ad. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.90 (95% CI: 0.19-4.39)

ae. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Al-Samkari 2020, Pesavento 2020

af. Baseline risks were calculated using the control group risks from the RCT and the following observational studies: Artifoni 2020, Campochiaro 2020, Kevorkian 2021, Martinelli 2021, Paolisso 2020, Piazza 2020

ag. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.74 (95% CI: 0.44-1.25)

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

ai. The ACTION trial reported on major adverse limb events, which was considered a surrogate outcome for limb amputation.

aj. Baseline risks were calculated using the control group risks from the RCT and the following observational studies: Arachchillage 2021, Artifoni 2020, Campochiaro 2020, Fortini 2020, Jimenez-Guiu 2020, Paolisso 2020, Pesavento 2020

ak. The 95% CI of the absolute effect includes both important harm and negligible benefit; effect estimate calculated based on a total of 4 events

al. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Piazza 2020

am. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.58 (95% CI: 0.13-2.61)

References

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