QUESTION

Should DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Therapeutic-intensity vs. Prophylactic-intensity be used for Patients with COVID-19 related acute illness who do not have suspected or confirmed VTE (PICO 2b)?

POPULATION:	Patients with COVID-19 related acute illness who do not have suspected or confirmed VTE (PICO 2b)
INTERVENTION:	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Therapeutic-intensity
COMPARISON:	Prophylactic-intensity
MAIN OUTCOMES:	All-cause mortality; Pulmonary embolism - Moderate severity; Deep Venous Thrombosis of the upper leg - Moderate severity; Major bleeding; Multiple organ failure; Ischemic stroke - Severe; Intracranial hemorrhage; Invasive mechanical ventilation - Long-term; Limb amputation; ICU hospitalization; ST-elevation myocardial infarction;
SETTING:	Inpatient
PERSPECTIVE:	Population
BACKGROUND:	Patients hospitalized with COVID-19 related acute illness may develop hemostatic abnormalities and hypercoagulability. Early studies demonstrated high rates of venous thrombotic complications. Furthermore, COVID-19 may be associated with arterial thrombotic complications and microvascular thrombosis, particularly in the lungs. The extent to which hypercoagulability contributes to respiratory failure and multiorgan failure remains unclear. Early reports suggested that patients with COVID-19 related acute illness have improved clinical outcomes with anticoagulant prophylaxis. However, the optimal intensity of anticoagulation and its effect on clinical outcomes is uncertain and there is substantial variation in clinical practice. References: 1. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18:2103-2109. 2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844-847. 3. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147. 4. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46:1089-1098. 5. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild Covid-19 infection. *J Thromb Haemost*. 2020;18:2031-2033. 6. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120-128. 7. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18:1094-1099. 8. Rosovsky RP, Sanfilippo KM, Wang TF, et al. Anticoagulation Practice Patterns in COVID-19: A Global Survey. Res Pract Thromb Haemost. 2020;4(6): 969-983.
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Angchaisuksiri, Blair, Cuker, Dane, Diuguid, Griffin, Klok, Lee, Mustafa, Neumann, A. Pai, Righini, Sanfilippo, Schünemann, Siegal, Skara, Terrell, Touri, Tseng. Two panel members (DeSancho, Kahn) were recused.

ASSESSMENT

Problem

Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**As of November 2021, COVID-19 has affected more than 250 million people. While many infected individuals remain asymptomatic, others develop severe illness requiring acute inpatient or outpatient care.** Patients with COVID-19 related acute illness may develop hemostatic abnormalities and hypercoagulability. Early studies demonstrated high rates of venous thrombotic complications. Furthermore, COVID-19 may be associated with arterial thrombotic complications and microvascular thrombosis, particularly in the lungs. Early reports have suggested that hospitalized medical patients with COVID-19 related acute illness may have improved clinical outcomes with anticoagulant prophylaxis. However, the optimal intensity of anticoagulation and its effect on clinical outcomes remains uncertain and there is substantial variation in clinical practice. References: 1. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18:2103-2109. 2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844-847. 3. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147. 4. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46:1089-1098. 5. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild Covid-19 infection. *J Thromb Haemost*. 2020;18:2031-2033. 6. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120-128. 7. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18:1094-1099. 8. Rosovsky RP, Sanfilippo KM, Wang TF, et al. Anticoagulation Practice Patterns in COVID-19: A Global Survey. Res Pract Thromb Haemost. 2020;4(6): 969-983.	The panel prioritized this question through question rating and discussions given the high perceived burden of thromboembolic disease or complications in COVID-19 patients. The benefits and harms of different intensity anticoagulation for preventive purposes are unclear.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Prophylactic-intensity	**Risk difference with DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Therapeutic-intensity**
All-cause mortality follow-up: range 5 days to 50 days[a,b]	3533 (5 RCTs)[1,2,3,4,5]	⨁◯◯◯ Very low[c,d,e]	**OR 0.78** (0.43 to 1.40)[f,g]	Low	
				70 per 1,000[h,i]	**15 fewer per 1,000** (39 fewer to 25 more)
				Moderate	
				96 per 1,000[j,h]	**20 fewer per 1,000** (52 fewer to 33 more)
				High	
				130 per 1,000[h,k]	**26 fewer per 1,000** (70 fewer to 43 more)
Pulmonary embolism - Moderate severity assessed with: Pulmonary embolism follow-up: range 4 days to 34 days[a,l]	3540 (5 RCTs)[1,2,3,4,5]	⨁⨁⨁◯ Moderate[m]	**OR 0.42** (0.25 to 0.71)	Low	
				16 per 1,000[i,n]	**9 fewer per 1,000** (12 fewer to 5 fewer)
				Moderate	
				30 per 1,000[j,n]	**17 fewer per 1,000** (22 fewer to 9 fewer)
				High	

The panel judged the desirable effects of the intervention to be small based on decision thresholds (see Appendix) indicating a small benefit with respect to mortality and multiorgan failure as well as additive trivial benefits on PE, DVT, invasive mechanical ventilation, and ICU admission. The panel acknowledged that there is likely to be significant overlap in these outcomes.

				55 per 1,000[k,n]	**31 fewer per 1,000** (41 fewer to 15 fewer)
Deep Venous Thrombosis of the upper leg - Moderate severity assessed with: Deep venous thrombosis follow-up: range 4 days to 34 days[a,o]	3540 (5 RCTs)[1,2,3,4,5]	⨁⨁◯◯ Low[m,p]	**OR 0.56** (0.22 to 1.41)	Low	
				5 per 1,000[i,q]	**2 fewer per 1,000** (4 fewer to 2 more)
				Moderate	
				9 per 1,000[i,q]	**4 fewer per 1,000** (7 fewer to 4 more)
				High	
				15 per 1,000[k,q]	**7 fewer per 1,000** (12 fewer to 6 more)
Multiple organ failure follow-up: mean 30 days[a,r]	700 (3 RCTs)[2,3,4]	⨁◯◯◯ Very low[s,t,u]	**OR 0.46** (0.03 to 6.59)	Low	
				17 per 1,000[i,v]	**9 fewer per 1,000** (16 fewer to 85 more)
				Moderate	
				50 per 1,000[i,v]	**26 fewer per 1,000** (48 fewer to 208 more)
				High	
				136 per 1,000[k,v]	**68 fewer per 1,000** (131 fewer to 373 more)
				Low	

Ischemic stroke - Severe assessed with: Ischemic stroke follow-up: range 5 days to 30 days[a,w]	3540 (5 RCTs)[1,2,3,4,5]	⨁⨁◯◯ Low[e,x]	**OR 0.92** (0.19 to 4.48)	1 per 1,000[j,y]	**0 fewer per 1,000** (1 fewer to 3 more)
				Moderate	
				4 per 1,000[j,y]	**0 fewer per 1,000** (3 fewer to 14 more)
				High	
				11 per 1,000[k,y]	**1 fewer per 1,000** (9 fewer to 36 more)
Invasive mechanical ventilation - Long-term assessed with: Invasive mechanical ventilation follow-up: range 7 days to 30 days[a,z]	700 (3 RCTs)[2,3,4]	⨁⨁◯◯ Low[d,aa]	**OR 0.69** (0.39 to 1.22)	Low	
				23 per 1,000[j,ab]	**7 fewer per 1,000** (14 fewer to 5 more)
				Moderate	
				53 per 1,000[j,ab]	**16 fewer per 1,000** (32 fewer to 11 more)
				High	
				118 per 1,000[k,ab]	**33 fewer per 1,000** (68 fewer to 22 more)
Limb amputation assessed with: Major adverse limb event follow-up: range 28 days to 30 days[ac,ad]	1314 (4 RCTs)[1,2,3,4]	⨁◯◯◯ Very low[ae,af]	**OR 0.33** (0.01 to 8.03)	Low	
				0 per 1,000[ag]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	

				2 per 1,000	**1 fewer per 1,000** (2 fewer to 14 more)
				High	
				12 per 1,000	**8 fewer per 1,000** (12 fewer to 77 more)
ICU hospitalization follow-up: range 3 days to 30 days[a,ah]	700 (3 RCTs)[2,3,4]	⨁⨁◯◯ Low[d,aa]	**OR 0.80** (0.52 to 1.23)	Low	
				45 per 1,000[i,ai]	**9 fewer per 1,000** (21 fewer to 10 more)
				Moderate	
				83 per 1,000[j,ai]	**15 fewer per 1,000** (38 fewer to 17 more)
				High	
				146 per 1,000[k,ai]	**26 fewer per 1,000** (64 fewer to 28 more)
ST-elevation myocardial infarction assessed with: Myocardial infarction follow-up: range 5 days to 30 days[a,aj]	3540 (5 RCTs)[1,2,3,4,5]	⨁⨁◯◯ Low[ak]	**OR 0.65** (0.14 to 2.97)	Low	
				1 per 1,000[i,al]	**0 fewer per 1,000** (1 fewer to 2 more)
				Moderate	
				4 per 1,000[j,al]	**1 fewer per 1,000** (3 fewer to 8 more)
				High	

				17 per 1,000[k,al]	**6 fewer per 1,000** (15 fewer to 32 more)

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

	e. 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 f. 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) g. 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) h. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 17 observational studies i. Lower bound of the 95% CI for the pooled mean event rate among baseline risk studies j. Pooled mean event rate among baseline risk studies k. Upper bound of the 95% CI for the pooled mean event rate among baseline risk studies l. 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 m. 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 n. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 9 observational studies 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 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 q. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 9 observational studies r. 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 s. Outcome in trial was multi-system organ failure as cause of death t. 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 u. Outcome data missing for two large RCTs, and one data from one trial represent multi-organ failure as primary cause of death	

	v. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from one RCT and 2 observational studies w. 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 x. 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 y. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 3 observational studies z. 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 aa. Outcome data missing for two large RCTs bb. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 6 observational studies cc. Follow-up duration for Lopes 2021, from which the baseline risk and effect estimate were used dd. 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 ee. Two trials reported on 'major adverse limb events', which was considered a surrogate outcome for limb amputation. ff. 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 gg. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs hh. 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 ii. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 7 observational studies jj. 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 kk. 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 ll. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 2 observational	

	studies	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Prophylactic-intensity	**Risk difference with DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Therapeutic-intensity**
Major bleeding follow-up: range 5 days to 30 days[a,b]	3541 (5 RCTs)[1,2,3,4,5]	⨁⨁⨁◯ Moderate[c,d]	**OR 1.79** (1.00 to 3.21)[e]	Low	
				6 per 1,000[f,g]	**5 more per 1,000** (0 fewer to 13 more)
				Moderate	
				12 per 1,000[h,f]	**9 more per 1,000** (0 fewer to 26 more)
				High	
				23 per 1,000[f,i]	**17 more per 1,000** (0 fewer to 47 more)
Intracranial hemorrhage follow-up: range 5 days to 30 days[a,j]	3540 (5 RCTs)[1,2,3,4,5]	⨁⨁◯◯ Low[k,l]	**OR 2.95** (0.12 to 72.74)	Low	
				0 per 1,000[g,m]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[h,m]	**0 fewer per 1,000** (0 fewer to 0 fewer)

ADDITIONAL CONSIDERATIONS

The panel judged the undesirable effects of the intervention to be trivial based on decision thresholds (see Appendix) indicating trivial harm with respect to major bleeding. The panel noted that the effect of the intervention on major bleeding did not cross the decision threshold between trivial and small (23 more major bleeding events per 1,000 patients) for any of the baseline risk groups presented in the evidence profile.

				High	
				10 per 1,000[i,m]	**19 more per 1,000** (9 fewer to 414 more)

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	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 e. 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) f. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 9 observational studies g. Lower bound of the 95% CI for the pooled mean event rate among baseline risk 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. 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 k. 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 l. 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 m. Baseline risks were calculated by pooling the risks among patients on prophylactic intensity anticoagulation from the RCTs and 2 observational studies	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Overall certainty based on the lowest certainty of any critical outcome according to GRADE.	The panel noted that an important source of uncertainty in the evidence is that much of it was collected in 2020 during an earlier phase of the pandemic. In light of changes in the affected patient population, circulating viral variants, and non-anticoagulant treatments (e.g., corticosteroids, monoclonal antibodies) for COVID-19 that have occurred over the course of the pandemic, it is uncertain to what extent earlier findings apply to the current phase of the pandemic.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The relative importance of the outcomes reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting less impairment and lower values reflecting greater impact on life. A systematic review of observational studies (11) suggests that affected people place a moderate relative value on avoiding pulmonary embolism, DVT, major bleeding and a low relative value (indicating great impairment on outcomes such as intracranial bleeds). There is moderate to high certainty in these findings. The evidence suggests that there is variability around these values or relative importance that the affected population places on these outcomes but this may be a result of the way they are measured. Below is the research evidence as synthesized. Survey results with ASH VTE guideline panels using visual analogue scales showed lower values than the one described below and this is explained by the fact that methods such as the standard gamble produce results that suggest less impairment of health. **The relative importance of the outcomes* was as follows in the identified studies:** **Pulmonary embolism: 0.63-0.93 (moderate certainty)** (2), (12), (1) - survey of ASH panelists: 0.25 for severe to 0.62 for mild) **Deep vein thrombosis: 0.64-0.99 (moderate certainty)** (2), (12), (1),(13), (14) - survey of ASH panelists: 0.43 for severe to 0.71 for mild) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off) (moderate certainty) (1) **Major bleeding as indicated by gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off) (moderate certainty) ((2, 1)) - survey of ASH panelists: 0.44) **Muscular bleeding:** 0.76 (time trade off) (moderate certainty) (1) **Minor intracranial bleeding event:** 0.75 (standard gamble) (high certainty) (2) **Major intracranial bleeding event:** 0.15 (standard gamble) (high certainty) (2) **Central nervous system bleeding:** 0.29-0.60 (standard gamble) (very low certainty) (3, 4) **Treatment with LMWH:** 0.993 (time trade off) (low certainty) (5)* indicated by utility value where 0 = death and 1.0 = full health **Studies described the following regarding the relative importance of outcomes and patients' preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis (6, 1, 7, 8) and that they would like to avoid adverse events but most of them are “not afraid of” the adverse events (9, 6, 4, 7, 8). Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; patients would like to avoid adverse events but most of them are “not afraid of” the adverse events. **Studies additionally described the following regarding the relative importance of outcomes and patients’ preferences for the pharmacological prophylaxis:** Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (10).	Panel members noted that there was possible uncertainty and variability in the relative value patients place on avoiding major bleeding events compared with reducing thrombotic events. One patient representative on the panel reported that he would potentially place a higher value on avoiding bleeding than on preventing a VTE event.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel judged that the balance of effects probably favors the intervention based on the small desirable effects, trivial undesirable effects, possibly important uncertainty or variability in how much people value the outcomes, and the very low certainty of the available data. The panel expressed concern that some of the trials included in the evidence profile enrolled patients early in the COVID-19 pandemic and that the applicability of the results to the current phase of the pandemic are unclear due to changes in the affected patient population, viral variants, and non-anticoagulant treatments (e.g., vaccines, corticosteroids, monoclonal antibody therapies). In addition, the panel noted that some of the trials preferentially included patients at increased risk of thrombosis and low risk of bleeding.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Cost of interventions (selected).** **Monthly (US) drug prices.** **<u>Prophylactic anticoagulation</u>** Apixaban 2.5 mg PO BID $493.19 Enoxaparin 30 mg subcutaneously $158.44 Enoxaparin 40 mg subcutaneously $164.25 Dalteparin 5,000 units subcutaneously $1,263.80 Heparin 5,000 units subcutaneously BID $44.33 Heparin 5,000 units subcutaneously TID $62.33 Fondaparinux 2.5 mg subcutaneously $333.92 Rivaroxaban 10 mg PO daily $486.81 https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html (Jul 20, 2021)	This comparison focused on differences in drug costs between prophylactic-intensity versus therapeutic-intensity anticoagulation. The panel noted that the specific agent and jurisdiction, rather than dose or intensity, are the primary drivers of the cost of anticoagulant drugs. For a given anticoagulant, while the total drug cost of the intervention would be higher than for the comparison, the panel felt that the difference would be negligible in comparison to the total costs of providing care for acutely ill patients with COVID-19.

	http://www.goodrx.com/ and https://www.drugs.com/price-guide/ (Jul 20, 2021)	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The prices listed above are drug prices for US resale. There should be little variation to these prices in the US.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence searched for because of the lack of high certainty data for effects and baseline risk.	Given the uncertainty about the effects of different intensities of anticoagulation in COVID-19 patients, cost-effectiveness analyses in non-COVID-19 patient populations may not be applicable.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified to address the impact on health equity.	The panel recognized that COVID-19 disproportionately affects certain segments of the general population including persons who identify as Black or Hispanic. However, the intervention was not felt to have a differential impact on health equity relative to the comparison.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Acceptability and use of higher versus lower intensity of pharmacological prophylaxis: With regards to different anticoagulants, we previously identified the following research that related to acceptability: Studies and surveys suggest the following regarding barriers associated with the intervention and its use across anticoagulants based on our 2018 review: A survey among 568 physicians and 825 patients from 5 countries showed that more patients considered injectable treatments effective than considered oral treatments effective (87% versus 76%, respectively). This trend was well predicted by the physicians (98% and 61%, respectively). Additionally, 46% of patients would accept an injectable treatment program lasting >2 months (67% for life-threatening diseases), a figure underestimated by physicians (11% and 46%, respectively). Overall, 73% of patients stated they would never miss an injection, whereas 54% of physicians expected patients to miss one injection in a month of therapy. (15) Among 250 hospitalized (surgical and medical) patients, initiation of prescribed therapy was 95% for LMWH, 88% for UFH 3/day and 87% for UFH 2/day. All scheduled doses were received by 77% on LMWH, 54% on UFH 3/day and 45% on UFH 2/day. Patient refusal explained 39% of omitted LMWH and 44% of omitted UFH doses. LMWH was less likely to be administered in surgical than in medical patients. (16)A survey among 1,553 Canadian health care providers showed that DVT prophylaxis was perceived as important by all provider groups, but this did not appear to translate into knowledge about underutilization of current DVT prophylaxis strategies. Physicians and pharmacists recognized the underuse of DVT prophylaxis in medical patients, while nurses and physiotherapists tended to perceive prophylaxis strategies as appropriate. Lack of clear indications and contraindications for prophylaxis and concerns about bleeding risks were perceived as important barriers. Preprinted orders were considered the most potentially successful and feasible way to optimize prophylaxis. (17) One large study using databases in the US found that the majority of at-risk hospitalized medically ill patients do not receive VTE prophylaxis. Only 18% of at-risk patients received VTE prophylaxis on day 1 or 2 in hospital, typically with LMWH (56% of patients receiving prophylaxis), pneumatic compression device (25%), vitamin K antagonist use (16%), or graduated compression stockings (11%). Use of prophylaxis exceeded 25% only in patients admitted from nursing homes and those with prior VTE. (18) Prescribing and uptake in different settings: Among 170 medical patients eligible for VTE prophylaxis, 54% received pharmacological VTE prophylaxis and 25% received non-	The acceptability of the intervention to various stakeholders (patients, healthcare providers, institutions, etc.) was considered. The intervention was felt to be acceptable to patients. The intervention was felt to be acceptable to providers. The panel acknowledged that given the very low certainty in evidence, there may be regional variation in acceptability of the intervention, particularly in regions where hospitalization rates for COVID-19 and baseline VTE risk may differ (e.g., Asian populations).

	pharmacological VTE prophylaxis due to a contraindication for pharmacological prophylaxis. (19) Among 64 medical patients, 59% received appropriate VTE prophylaxis using LMWH. (20)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Feasibility of using higher versus lower intensity of anticoagulants. Feasibility and use of any pharmacological prophylaxis: Studies showed the following barriers to utilizing the intervention/option: Among 1,894 acutely ill medical patients from 29 Canadian hospitals, 23% received some form of VTE prophylaxis, but only 16% received appropriate prophylaxis. Factors independently associated with greater use of prophylaxis included internist (vs. other specialty) as attending physician, university-associated (vs. community) hospital, immobilization, presence of >1 VTE risk factors, and duration of hospitalization, however, use of prophylaxis was unacceptably low in all groups. (21)A survey among ICU directors, bedside pharmacists, thromboprophylaxis research coordinators and physician site investigators in 27 Canadian ICU's, showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. Top five reported facilitators were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. Acceptability of facilitators varied across ICU's. (22)	The intervention was felt to be feasible as differing intensities of anticoagulation are already used broadly in the management of acutely ill patients with COVID-19.(Rosovsky et al., 2020)

SUMMARY OF JUDGEMENTS

CRITERIA	JUDGEMENT	IMPORTANCE FOR DECISION
PROBLEM	Yes	
DESIRABLE EFFECTS	Small	
UNDESIRABLE EFFECTS	Trivial	
CERTAINTY OF EVIDENCE	Very low	
VALUES	Possibly important uncertainty or variability	
BALANCE OF EFFECTS	Probably favors the intervention	
RESOURCES REQUIRED	Negligible costs and savings	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies	

CRITERIA	JUDGEMENT	IMPORTANCE FOR DECISION
COST EFFECTIVENESS	No included studies	
EQUITY	Probably no impact	
ACCEPTABILITY	Probably yes	
FEASIBILITY	Yes	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

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).

Remarks:

- Patients with COVID-19–related acute illness are defined as those with clinical features that would typically result in admission to a medicine inpatient ward without requirement for advanced clinical support. Examples include patients with dyspnea or mild to moderate hypoxia.
- An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Risk-assessment models to estimate thrombotic risk in hospitalized patients have been validated in COVID-19 patients, with modest prognostic performance. No risk assessment models for bleeding have been validated in COVID-19 patients. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at high bleeding risk and low thrombotic risk.
- At present, there is no direct high-certainty evidence comparing different types of anticoagulants in patients with COVID-19. Unfractionated or low molecular weight heparin may be preferred because of a preponderance of evidence with these agents. There are no studies of therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population.

Justification

Overall justification

The panel judged the overall certainty of evidence of effects to be very low although the panel considered the certainty of evidence to be somewhat higher for pulmonary embolism and major bleeding than for all other outcomes. The undesirable effects of the intervention were considered trivial, driven by a trivial effect on major bleeding. The desirable effects of the intervention were considered small, driven by small effects on mortality and multiorgan failure and additive trivial effects on PE, DVT, invasive mechanical ventilation, and ICU admission. The panel also noted that there is possibly important uncertainty or variability in how people value outcomes, whereby some patients may place greater value on avoiding major bleeding than avoiding a thromboembolic event. Based on these judgments, the panel suggested therapeutic-intensity anticoagulation over prophylactic-intensity anticoagulation in acutely ill medical patients with COVID-19, while acknowledging that individualized decision-making is required. The conditional recommendation for the intervention was not unanimous: 8 panelists voted for a conditional recommendation in favor of therapeutic-intensity anticoagulation, 4 panelists voted for a conditional recommendation in favor of prophylactic-intensity anticoagulation, 4 panelists voted for a conditional recommendation in favor of either therapeutic- or prophylactic-intensity anticoagulation, and 3 panelists abstained, underscoring the uncertainty in the evidence. This recommendation will continue to be updated based on living reviews of evolving evidence.

Detailed justification

Balance of effects

The use of decision thresholds allowed the panel to quantify the magnitude of effect per outcome to come to an overall judgement on the balance of health effects. Among desirable effects, the small reductions in all-cause mortality and multiorgan failure were of very low certainty due to serious inconsistency in the effects across included trials and very serious imprecision in the pooled absolute effect for mortality, and serious risk of bias, serious indirectness, and very serious imprecision for multiorgan failure. The evidence for a reduction in PE was more certain (moderate), but of trivial magnitude based on the relatively low baseline risk of PE. All other outcomes showed reductions of trivial magnitude based on low certainty evidence (deep venous thrombosis, invasive mechanical ventilation, ICU admission) or very low certainty evidence (ischemic stroke, ST-elevation myocardial infarction, limb amputation). At least some of these outcomes can be considered independent, and therefore the panel judged that on aggregate the desirable effects were of small magnitude. There was moderate certainty in the undesirable effect of therapeutic-intensity anticoagulation in increasing the risk of major bleeding. However, the panel judged this effect to be of trivial magnitude based on decision

thresholds and the relatively low mean baseline risk from included studies. The panel expressed concerns about the potential morbidity of anticoagulant-associated major bleeding events and possible underestimation of the absolute risk of major bleeding due to exclusion of patients at high bleeding risk from some clinical trials. The effect on intracranial hemorrhage was highly uncertain as this was calculated based on one event. The panel also noted that an important limitation in the evidence is that much of it was collected in 2020 during an earlier phase of the pandemic. In light of changes in the affected patient population, circulating viral variants, and non-anticoagulant treatments (e.g., corticosteroids, monoclonal antibodies) for COVID-19 that have occurred over the course of the pandemic, it is uncertain to what extent earlier findings apply to the current phase of the pandemic. Weighing the uncertainty in the included evidence and changes that have occurred over the course of the pandemic, the panel judged that the potential desirable effects of therapeutic-intensity anticoagulation probably outweigh the potential undesirable effects. The panel, however, acknowledged the potential for harm, and noted that an individualized decision is important for each patient based on an assessment of thrombotic and bleeding risk. The panel emphasized that there is still a need for large high-quality randomized controlled trials to increase the certainty in the evidence for multiple critical outcomes.

Subgroup considerations

Assessment using the ICEMAN instrument indicated that the subgroup effect of DOACs (rivaroxaban) vs heparins (UFH or LMWH) on mortality had low credibility (see manuscript appendix), and the overall effect is reported. The panel acknowledges that this potential subgroup effect may become credible with additional evidence.

Implementation considerations

Risk-assessment models to estimate thrombotic risk in hospitalized patients have been validated in COVID-19 patients, with modest prognostic performance. No risk assessment models for bleeding have been validated in COVID-19 patients. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at low thrombotic risk and high bleeding risk.

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Monitoring and evaluation

Patients receiving prophylactic-intensity, intermediate-intensity, or therapeutic-intensity anticoagulation therapy require regular reassessment of thrombotic and bleeding risk. It is important to frequently assess and optimize factors that affect the safety of anticoagulation therapy (e.g., renal function, thrombocytopenia, blood pressure control, minimizing concomitant antiplatelet therapy). Frequent clinical assessments for signs and symptoms of thromboembolism and bleeding are also necessary in acutely ill patients.

The panel did not specifically address the use of anticoagulant monitoring with anti-Xa levels, or the use of screening lower extremity ultrasonography in asymptomatic patients. However, these measures are not routinely recommended for monitoring acutely ill patients receiving anticoagulation therapy.

References:

1. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv* 2018; 2(22): 3257-3291.

Research priorities

- Studies assessing baseline VTE risk, major bleeding risk, and mortality in acutely ill patients on prophylactic-intensity anticoagulation therapy
- Studies examining the impact of non-anticoagulant interventions (e.g., vaccines, corticosteroids, antiviral therapies, antiplatelet therapies, anticytokine therapies, monoclonal antibody therapies) on thrombotic risk
- Studies examining the impact of different viral variants on thrombotic risk
- Development and validation of risk assessment models for thrombosis and bleeding in patients with COVID-19 related acute illness
- Studies examining the impact of anticoagulant therapy on thrombosis and bleeding outcomes in patients of differing race/ethnicity
- Studies comparing mortality, thrombosis, bleeding, and functional outcomes with different available anticoagulant agents and intensities
- Studies estimating the relative disutility of thrombotic and bleeding outcomes in patients with COVID-19 related acute illness

REFERENCES SUMMARY

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Appendix. Absolute effect decision thresholds

		Decision Thresholds		
Outcome	**Utility Value**	**Trivial/Small**	**Small/Moderate**	**Moderate/Large**
	Mean (SD)	**Events per 1000 (95% CI)**		
Mortality	0	16 (9 to 22)	31 (22 to 39)	60 (46 to 73)
PE – Moderate	0.42 (0.15)	27 (15 to 38)	53 (38 to 68)	103 (80 to 125)
Proximal DVT – Moderate	0.58 (0.14)	37 (21 to 53)	73 (53 to 94)	142 (110 to 173)
Major Bleeding	0.33 (0.23)	23 (13 to 33)	46 (33 to 59)	89 (69 to 109)
Ischemic Stroke - Severe	0.14 (0.10)	18 (10 to 26)	36 (26 to 46)	69 (54 to 85)
Intracranial Hemorrhage	0.12 (0.10)	18 (10 to 25)	35 (25 to 45)	68 (53 to 83)
Multiple Organ Failure	0.15 (0.14)	18 (10 to 26)	36 (26 to 46)	70 (54 to 86)
ST Elevation MI (STEMI)	0.31 (0.19)	23 (13 to 32)	44 (32 to 57)	86 (67 to 105)
Limb Amputation	0.26 (0.16)	21 (12 to 30)	41 (30 to 53)	80 (63 to 98)
ICU Hospitalization	0.38 (0.16)	25 (14 to 36)	50 (36 to 63)	96 (75 to 117)
Long-Term Invasive Ventilation	0.20 (0.12)	20 (11 to 28)	38 (28 to 49)	74 (58 to 91)