QUESTION

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

POPULATION:	Patients with COVID-19 related acute illness who do not have suspected or confirmed VTE (PICO 2a)
INTERVENTION:	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Intermediate-intensity
COMPARISON:	Prophylactic-intensity
MAIN OUTCOMES:	All-cause mortality; Pulmonary embolism; Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT); Major bleeding; Multiple organ failure; Ischemic stroke (severe); Intracranial hemorrhage; Invasive ventilation; 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 April 2022, COVID-19 has affected more than 500 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.	

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 Intermediate-intensity
Pulmonary embolism follow-up: range 4 days to 34 days[a]	248 (2 RCTs)[1,2]	⨁◯◯◯ Very low[b,c]	**OR 0.42** (0.01 to 11.96)	Low	
				18 per 1,000[d]	**10 fewer per 1,000** (18 fewer to 162 more)
				Moderate	
				32 per 1,000[e]	**18 fewer per 1,000** (32 fewer to 251 more)
				High	
				56 per 1,000[f]	**32 fewer per 1,000** (55 fewer to 359 more)
Invasive ventilation follow-up: range 28 days to 30 days[a]	248 (2 RCTs)[1,2]	⨁◯◯◯ Very low[g]	**OR 0.99** (0.39 to 2.50)	Low	
				45 per 1,000[d]	**0 fewer per 1,000** (27 fewer to 60 more)
				Moderate	
				74 per 1,000[e]	**1 fewer per 1,000** (44 fewer to 93 more)
				High	
				119 per 1,000[f]	**1 fewer per 1,000** (69 fewer to 133 more)

All desirable effects, including pulmonary embolism, were of trivial magnitude when decision thresholds were applied.

ST-elevation myocardial infarction follow-up: range 5 days to 30 days	248 (2 RCTs)[1,2]	⨁◯◯◯ Very low[h]	**OR 0.32** (0.03 to 3.16)	Low	
				2 per 1,000[d]	**1 fewer per 1,000** (2 fewer to 4 more)
				Moderate	
				6 per 1,000[e]	**4 fewer per 1,000** (6 fewer to 13 more)
				High	
				17 per 1,000[f]	**11 fewer per 1,000** (16 fewer to 35 more)

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.

a. Follow up durations from the observational studies informing the baseline risk
b. The 95% CI of the absolute effect includes both large harm and small benefit
c. Both trials were open-label, and one trial had unblinded outcome assessors
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. The 95% CI of the absolute effect includes both moderate benefit and large harm
h. The pooled effect estimate is based on a total of only two events

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Large
○ Moderate
○ Small
○ Trivial
○ 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 Intermediate-intensity**
All-cause mortality follow-up: range 5 days to 34 days[a]	248 (2 RCTs)[1,2]	⨁◯◯◯ Very low[b,c]	**OR 2.21** (0.69 to 7.03)	Low	
				67 per 1,000[d]	**70 more per 1,000** (20 fewer to 268 more)
				Moderate	
				91 per 1,000[e]	**90 more per 1,000** (26 fewer to 322 more)
				High	
				123 per 1,000[f]	**114 more per 1,000** (35 fewer to 373 more)
Major bleeding follow-up: range 5 days to 90 days[a]	248 (2 RCTs)[1,2]	⨁◯◯◯ Very low[c,g]	**OR 1.01** (0.06 to 16.41)	Low	
				6 per 1,000[d]	**0 fewer per 1,000** (6 fewer to 84 more)
				Moderate	
				11 per 1,000[e]	**0 fewer per 1,000** (10 fewer to 143 more)
				High	

Judgment primarily based on a large increase in all-cause mortality.

				21 per 1,000[f]	**0 fewer per 1,000** (20 fewer to 239 more)
Multiple organ failure follow-up: mean 30 days	182 (1 RCT)[2]	⨁◯◯◯ Very low[g]	**OR 1.53** (0.25 to 9.40)	Study population	
				22 per 1,000	**11 more per 1,000** (16 fewer to 152 more)
Ischemic stroke (severe) assessed with: any stroke follow-up: range 5 days to 30 days	248 (2 RCTs)[1,2]	⨁◯◯◯ Very low[g,h]	**OR 1.37** (0.09 to 20.07)	Low	
				2 per 1,000[d]	**1 more per 1,000** (2 fewer to 37 more)
				Moderate	
				4 per 1,000[e]	**1 more per 1,000** (4 fewer to 71 more)
				High	
				10 per 1,000[f]	**4 more per 1,000** (9 fewer to 159 more)
ICU hospitalization follow-up: range 3 days to 30 days	183 (1 RCT)[2]	⨁◯◯◯ Very low[i]	**OR 1.01** (0.31 to 3.26)	Low	
				61 per 1,000	**1 more per 1,000** (41 fewer to 114 more)
				Moderate	
				94 per 1,000	**1 more per 1,000** (63 fewer to 159 more)
				High	

				141 per 1,000	**1 more per 1,000** (93 fewer to 208 more)

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.

a. Follow up durations from the observational studies informing the baseline risk
b. The 95% CI of the absolute effect includes both large harm and small benefit
c. Both trials were open-label, and one trial had unblinded outcome assessors, but unlikely to have affected this outcome
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. The 95% CI of the absolute effect includes both trivial benefit and large harm
h. Both trials were open-label, and one trial had unblinded outcome assessors
i. The 95% CI of the absolute effect includes both moderate benefit and large harm

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 certainty of the evidence for all critical outcomes was very low.

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.

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 large potential harms outweigh the trivial potential benefits, and the balance of effects probably favors prophylactic-intensity anticoagulation.

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 twice daily $566.55 Enoxaparin 30 mg subcutaneously once daily $185.00 Enoxaparin 40 mg subcutaneously once daily $186.25 Dalteparin 5,000 units subcutaneously once daily $1,292.65 Heparin 5,000 units subcutaneously twice daily $47.57 Heparin 5,000 units subcutaneously three times daily $67.10 Fondaparinux 2.5 mg subcutaneously once daily $313.20 Rivaroxaban 10 mg PO once daily $523.12 https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html (Apr 25, 2022) http://www.goodrx.com/ and https://www.drugs.com/price-guide/ (Apr 25, 2025)	This comparison focused on differences in drug costs between prophylactic-intensity versus intermediate-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.

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	These are listed drug prices for US resale. There should be little variation to these prices in the US.	Prices and specific low molecular weight heparins may vary between different countries.

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		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 Blacks and Hispanics. 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 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

	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-pharmacological VTE prophylaxis due to a contraindication for pharmacological prophylaxis. (19) Among 64 medical patients, 59% received appropriate VTE prophylaxis using LMWH. (20)	for COVID-19 and baseline VTE risk may differ (e.g., Asian populations).

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 without COVID-19.

SUMMARY OF JUDGEMENTS

CRITERIA		IMPORTANCE FOR DECISION
PROBLEM	Yes	
DESIRABLE EFFECTS	Trivial	
UNDESIRABLE EFFECTS	Large	
CERTAINTY OF EVIDENCE	Very low	
VALUES	Possibly important uncertainty or variability	
BALANCE OF EFFECTS	Probably favors the comparison	
RESOURCES REQUIRED	Negligible costs and savings	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies	
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 prophylactic-intensity over intermediate-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.
- A separate recommendation (2B) addresses the comparison of therapeutic-intensity and prophylactic-intensity anticoagulation in acutely ill COVID-19 patients (https://guidelines.ash.gradepro.org/profile/YmZiP8YDDNA).
- 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.

Justification

Overall justification

The panel judged the overall certainty of evidence of effects to be very low. The undesirable effects of intermediate-intensity anticoagulation were considered large, driven by a large increase in all-cause mortality. The desirable effects of intermediate-intensity anticoagulation were considered trivial, driven by a trivial effect on pulmonary embolism. 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 prophylactic-intensity anticoagulation over intermediate-intensity anticoagulation in acutely ill medical patients with COVID-19, while acknowledging that individualized decision-making is required. 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 trivial reductions in pulmonary embolism, ST-elevation myocardial infarction, and invasive mechanical ventilation were of very low certainty primarily due to extremely serious imprecision. There was also very low certainty in the undesirable effect of intermediate-intensity anticoagulation regarding a large increase in all-cause mortality, trivial increase in multiple organ failure and ischemic stroke, and no effect on major bleeding. 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 clinical trials. The effects on deep venous thrombosis in the upper leg, intracranial hemorrhage, and limb amputation were unknown as no events were observed in the trials. Taken together, the panel judged that the balance of effects probably favoured prophylactic-intensity anticoagulation. The panel also noted that 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 all critical outcomes.

Subgroup considerations

No subgroup considerations.

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 higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding risk.

References:

1. Barbar S, Noventa F, Rossetto V, et al. A risk asssment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost* 2010; 8: 2450-2457.

2. Spyropoulos AC, Anderson FA Jr, Fitzgerald G, et al. IMPROVE Investigators. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest* 2011; 140: 706-714.

3. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest* 2011; 139: 69-79.

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; this includes temporal trends in event rates
- 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
- Studies assessing to what extent there is equipoise in clinical practice regarding the use of intermediate-intensity anticoagulation, and if this applies to specific subgroups

REFERENCES SUMMARY

1. Locadia, M., Bossuyt, P. M., Stalmeier, P. F., Sprangers, M. A., van Dongen, C. J., Middeldorp, S., Bank, I., van der Meer, J., Hamulyak, K., Prins, M. H.. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost; Dec 2004.
2. Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., Wells, P.. Estimating quality of life in acute venous thrombosis. JAMA Intern Med; Jun 24 2013.
3. Lenert, L. A., Soetikno, R. M.. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc; Jan-Feb 1997.
4. O'Meara, J. J.,3rd, McNutt, R. A., Evans, A. T., Moore, S. W., Downs, S. M.. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. N Engl J Med; Jun 30 1994.
5. Marchetti, M., Pistorio, A., Barone, M., Serafini, S., Barosi, G.. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. American Journal of Medicine; Aug 2001.
6. Haac, B,E., O'Hara, N,N., Mullins, D,C., Stein, D,M., Manson, T,T., Johal, M., Castillo, R., O'Toole, R,V., Slobogean, G,P.. Patient preferences for venous thromboembolism prophylaxis after injury. 2016.
7. Quante, M., Thate-Waschke, I., Schofer, M.. [What are the reasons for patient preference? A comparison between oral and subcutaneous administration]. Z Orthop Unfall; Sep 2012.
8. Wong, A., Kraus, P. S., Lau, B. D., Streiff, M. B., Haut, E. R., Hobson, D. B., Shermock, K. M.. Patient preferences regarding pharmacologic venous thromboembolism prophylaxis. Journal of Hospital Medicine (Online); Feb 2015.
9. Barcellona, D., Contu, P., Sorano, G. G., Pengo, V., Marongiu, F.. The management of oral anticoagulant therapy: the patient's point of view. Thromb Haemost; Jan 2000.
10. Maxwell, G. L., Synan, I., Hayes, R. P., Clarke-Pearson, D. L.. Preference and compliance in postoperative thromboembolism prophylaxis among gynecologic oncology patients. Obstet Gynecol; Sep 2002.
11. Etxeandia-Ikobaltzeta, I., , Zhang,Y., , Brundisini,F., , Florez,I., Wiercioch, W., Nieuwlaat, R., Begum, H., Cuello, C., Roldan, Y., Chen, R., Ding, C., Morgan, R., Riva, J., Zhang, Y., Charide, R., Agarwal, A., Balduzzi, S., Morgano, GP., Yepes-Nuñez, J., Rehman, Y., Neumann, I., Schwab, N., Baldeh, T., Braun, C., Rodríguez, MF., Schünemann, HJ. Patient values and preferences regarding VTE disease: a systematic review to inform American Society of Hematology guidelines. Blood Adv; 2020.
12. Hogg, K., Shaw, J., Coyle, D., Fallah, P., Carrier, M., Wells, P.. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thromb Res; Oct 2014.
13. Marvig, C. L., Verhoef, T. I., de Boer, A., Kamali, F., Redekop, K., Pirmohamed, M., Daly, A. K., Manolopoulos, V. G., Wadelius, M., Bouvy, M., Maitland-van der Zee, A. H.. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thromb Res; Jul 2015.
14. Utne, K. K., Tavoly, M., Wik, H. S., Jelsness-Jorgensen, L. P., Holst, R., Sandset, P. M., Ghanima, W.. Health-related quality of life after deep vein thrombosis. Springerplus; 2016.
15. Cimminiello, C., Anderson, F. A.,Jr.. Physician and patient perceptions of the route of administration of venous thromboembolism prophylaxis: results from an international survey. Thromb Res; Feb 2012.
16. Fanikos, J., Stevens, L. A., Labreche, M., Piazza, G., Catapane, E., Novack, L., Goldhaber, S. Z.. Adherence to pharmacological thromboprophylaxis orders in hospitalized patients. American Journal of Medicine; Jun 2010.
17. Lloyd, N.S., Douketis, J.D, Cheng, J., Schu¨nemann, H.J., Cook, D.J., Thabane, L., Pai, M., Spencer, F.A., Haynes, B.R.. Barriers and Potential Solutions Toward Optimal Prophylaxis Against Deep Vein Thrombosis for Hospitalized Medical Patients: a Survey of Healthcare Professionals. Journal of Hospital Medicine; 2012.
18. Pendergraft, T., Liu, X., Edelsberg, J., Phatak, H., Vera-Llonch, M., Liu, L. Z., Oster, G.. Prophylaxis against venous thromboembolism in hospitalized medically ill patients. Circulation. Cardiovascular Quality & Outcomes; Jan 1 2013.
19. Panju, M., Raso, D., Patel, A., Panju, A., Ginsberg, J.. Evaluation of the use of venous thromboembolism prophylaxis in hospitalised medical patients. Journal of the Royal College of Physicians of Edinburgh; Dec 2011.
20. Eijgenraam, P., Meertens, N., van den Ham, R., Ten Cate, H., Ten Cate-Hoek, A. J.. The effect of clinical decision support on adherence to thrombosis prophylaxis guidelines in medical patients; a single center experience. Thromb Res; Mar 2015.
21. Kahn, S.R.,Panju,A.,Geerts,W.,Pineo,G.F.,Desjardins,L.,Turpie,A.G.,Glezer,S.,Thabane,L.,Sebaldt,R. J.. Multicenter evaluation of the use of venous thromboembolism prophylaxis in acutely ill medical patients in Canada. Thrombosis Research; 2007.
22. Cook, D., Duffett, M., Lauzier, F., Ye, C., Dodek, P., Paunovic, B., Fowler, R., Kho, M. E., Foster, D., Stelfox, T., Sinuff, T., Zytaruk, N., Clarke, F., Wood, G., Cox, M., Kutsiogiannis, J., Jacka, M., Roussos, M., Kumar, H., Guyatt, G., Investigators, Conecckt-,T., Canadian Critical Care Trials, Group. Barriers and facilitators of thromboprophylaxis for medical-surgical intensive care unit patients: a multicenter survey. J Crit Care; Jun 2014.