QUESTION

Should prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux vs. no anticoagulation be used for post-discharge thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation?	
POPULATION:	patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation
INTERVENTION:	prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux
COMPARISON:	no anticoagulation
MAIN OUTCOMES:	Mortality; Pulmonary Embolism; Deep Venous Thrombosis; Venous Thromboembolism; Major Bleeding; Ischemic Stroke; ST-elevation Myocardial Infarction; Readmission
SETTING:	Hospital discharge
PERSPECTIVE:	Population
BACKGROUND:	
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): No panel members 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 February 2022, COVID-19 has affected more than 440 million people. While many infected individuals remain asymptomatic, others develop severe illness requiring critical care.** Patients with COVID-19 related critical 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 critical illness have improved clinical outcomes with anticoagulant prophylaxis. However, the optimal intensity of anticoagulation and its effect on clinical outcomes is uncertain. 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.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ 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 no anticoagulation	Risk difference with prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux
Mortality follow-up: range <30 days to 92 days[a]	318 (1 RCT)[1]	⨁◯◯◯ Very low[b,c]	**OR 0.75** (0.16 to 3.38)	Low	
				14 per 1,000[d]	**3 fewer per 1,000** (12 fewer to 32 more)
				Mean	
				25 per 1,000[e]	**6 fewer per 1,000** (21 fewer to 55 more)

ADDITIONAL CONSIDERATIONS

The panel remarked that the absolute effect on PE had some overlap with all-cause mortality. The panel judged that the aggregate of the desirable effects on critical outcomes would be of Trivial magnitude.

				High	
				44 per 1,000[f]	**11 fewer per 1,000** (37 fewer to 91 more)
Pulmonary Embolism follow-up: range <30 days to 92 days[g]	318 (1 RCT)[1]	⨁◯◯◯ Very low[h,i]	**OR 0.19** (0.02 to 1.69)	Low	
				3 per 1,000[d]	**2 fewer per 1,000** (3 fewer to 2 more)
				Mean	
				7 per 1,000[e]	**6 fewer per 1,000** (7 fewer to 5 more)
				High	
				20 per 1,000[f]	**16 fewer per 1,000** (20 fewer to 13 more)
Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) follow-up: range <30 days to 92 days[j]	318 (1 RCT)[1]	⨁◯◯◯ Very low[h,k]	**OR 0.14** (0.01 to 2.74)	Low	
				1 per 1,000[d]	**1 fewer per 1,000** (1 fewer to 2 more)
				Mean	
				3 per 1,000[e]	**3 fewer per 1,000** (3 fewer to 5 more)
				High	
				12 per 1,000[f]	**10 fewer per 1,000**

					(12 fewer to 20 more)
Ischemic Stroke follow-up: range 35 days to 92 days[l]	318 (1 RCT)[1]	⨁◯◯◯ Very low[m,n]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				4 per 1,000[o]	**4 fewer per 1,000** (4 fewer to 4 fewer)
ST-elevation Myocardial Infarction assessed with: Myocardial Infarction follow-up: range 35 days to 92 days[p]	318 (1 RCT)[1]	⨁◯◯◯ Very low[m,n]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				5 per 1,000[q]	**5 fewer per 1,000** (5 fewer to 5 fewer)
Readmission follow-up: range 35 days to 92 days	318 (1 RCT)[1]	⨁⨁◯◯ Low[r]	**OR 0.20** (0.01 to 4.15)	Study population	
				13 per 1,000	**10 fewer per 1,000** (12 fewer to 38 more)
				High	
				155 per 1,000[s]	**120 fewer per 1,000** (153 fewer to 277 more)

1. Ramacciotti, E., Barile Agati, L., Calderaro, D., Aguiar, V. C. R., Spyropoulos, A. C., de Oliveira, C. C. C., Lins Dos Santos, J., Volpiani, G. G., Sobreira, M. L., Joviliano, E. E., Bohatch Junior, M. S., da Fonseca, B. A. L., Ribeiro, M. S., Dusilek, C., Itinose, K., Sanches, S. M. V., de Almeida Araujo Ramos, K., de Moraes, N. F., Tierno, Pfgmm, de Oliveira, Alml, Tachibana, A., Chate, R. C., Santos, M. V. B., de Menezes Cavalcante, B. B., Moreira, R. C. R., Chang, C., Tafur, A., Fareed, J., Lopes, R. D., investigators, Michelle. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet; Jan 1 2022.

a. 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
b. The MICHELLE trial included patients at high risk of VTE and low risk of bleeding. It is unclear what proportion of all discharged COVID-19 patients this represents.
c. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes small benefit and moderate harm; rated down 3 levels for extremely serious imprecision
d. Lower boundary of 95% CI of pooled baseline risk analysis
e. Mean of pooled baseline risk analysis
f. Higher boundary of 95% CI of pooled baseline risk analysis
g. 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
h. The effect estimate is based on few events; rated down 2 levels for very serious imprecision
i. Patients and providers were not blinded to group allocation and it is unclear if test ordering was balanced during the trial. The CTPA that was planned in all patients at 35 days, but performed in <80%, was assumed to primarily capture asymptomatic events
j. 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
k. Patients and providers were not blinded to group allocation and it is unclear if test ordering was balanced during the trial. The US that was planned in all patients at 35 days, but performed in <80%, was assumed to primarily capture asymptomatic events
l. 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
m. No events observed in the trial; rated down 2 levels for very serious imprecision
n. Patients and providers were not blinded to group allocation and it is unclear if test ordering was balanced during the trial
o. One observational study reporting 0.4% ischemic stroke during 92 days follow-up.
p. 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

q. One observational study reporting 0.5% myocardial infarction during 92 days follow-up.
r. The 95% CI of the absolute effect estimate includes important benefit and important harm; rated down 3 levels for very serious imprecision
s. One baseline risk study reported 15.5% readmission during 92 days follow-up

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 no anticoagulation	Risk difference with prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux
Major Bleeding follow-up: range 35 days to 92 days[a]	318 (1 RCT)[1]	⨁⨁◯◯ Low[b]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Low	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				16 per 1,000[d]	**16 fewer per 1,000** (16 fewer to 16 fewer)
NON-COVID acutely ill - Major Bleeding[a]	27794 (4 RCTs)[2,3,4,5]	⨁⨁◯◯ Low[e]	**RR 2.09** (1.33 to 3.27)	Low	
				4 per 1,000	**4 more per 1,000** (1 more to 9 more)

ADDITIONAL CONSIDERATIONS

The effect on major bleeding in COVID-19 patients could not be calculated due to no observed events in the randomized controlled trial. Based on the absolute effect in non-COVID-19 patients, the panel judged the undesirable effect to be of Trivial magnitude.

				High	
				12 per 1,000[f]	**13 more per 1,000** (4 more to 27 more)

1. Ramacciotti, E., Barile Agati, L., Calderaro, D., Aguiar, V. C. R., Spyropoulos, A. C., de Oliveira, C. C. C., Lins Dos Santos, J., Volpiani, G. G., Sobreira, M. L., Joviliano, E. E., Bohatch Junior, M. S., da Fonseca, B. A. L., Ribeiro, M. S., Dusilek, C., Itinose, K., Sanches, S. M. V., de Almeida Araujo Ramos, K., de Moraes, N. F., Tierno, Pfgmm, de Oliveira, Alml, Tachibana, A., Chate, R. C., Santos, M. V. B., de Menezes Cavalcante, B. B., Moreira, R. C. R., Chang, C., Tafur, A., Fareed, J., Lopes, R. D., investigators, Michelle. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet; Jan 1 2022.
2. Hull, R. D., Schellong, S. M., Tapson, V. F., Monreal, M., Samama, M. M., Nicol, P., Vicaut, E., Turpie, A. G., Yusen, R. D., study, Exclaim. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med; Jul 6 2010.
3. Goldhaber, S. Z., Leizorovicz, A., Kakkar, A. K., Haas, S. K., Merli, G., Knabb, R. M., Weitz, J. I., Investigators, Adopt,Trial. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med; Dec 8 2011.
4. Cohen, A. T., Spiro, T. E., Buller, H. R., Haskell, L., Hu, D., Hull, R., Mebazaa, A., Merli, G., Schellong, S., Spyropoulos, A. C., Tapson, V., Investigators, Magellan. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med; Feb 7 2013.
5. Cohen, A. T., Harrington, R. A., Goldhaber, S. Z., Hull, R. D., Wiens, B. L., Gold, A., Hernandez, A. F., Gibson, C. M., Investigators, Apex. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med; Aug 11 2016.

a. The decision thresholds for Major Bleeding were: 23 per 1,000 for Trivial/Small; 46 per 1,000 for Small/Moderate; 89 per 1,000 for Moderate/Large
b. No events observed in the trial; rated down 2 levels for very serious imprecision
c. Three of four baseline risk studies reported 0% Major bleeding
d. One baseline risk study reported 1.6% major bleeding during 92 days follow-up
e. Very serious indirectness. Evidence from non-COVID-19 patients; Indirect comparison of interventions although no different effects observed in sensitivity analysis
f. Decousus (2011) reports on incidence of in hospital bleeding in patients who were not bleeding at admission and had data regarding bleeding during the 3 months prior to admission (n=10,866) based on data from the International Medical Prevention Registry on Venous

	Thromboembolism (IMPROVE) from July 2002 and September 2006	

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		There was consensus among the panel that the overall certainty of evidence for desirable and undesirable effects was very low. Depending on the outcome, this was primarily due to very serious or extremely serious imprecision, serious risk of bias, and/or serious indirectness.

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 (10) 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 (3), (11), (1) - survey of ASH panelists: 0.25 for severe to 0.62 for mild) **Deep vein thrombosis:** 0.64-0.99 (3), (11), (12), (13) - 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) (1) **Major bleeding as indicated by gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off) (3), (1) - survey of ASH panelists: 0.44)	The panel judged that the relative importance of the outcomes will not be different compared to patients not diagnosed with COVID-19 but that there is possibly important uncertainty or variability about the value they assign to different outcomes.

	Muscular bleeding: 0.76 (time trade off) (1) **Minor intracranial bleeding event:** 0.75 (standard gamble) (3) **Major intracranial bleeding event:** 0.15 (standard gamble) (3) **Central nervous system bleeding:** 0.29-0.60 (standard gamble) (6), (4) **Treatment with LMWH:** 0.993 (time trade off) (9)* 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 (2), (1), (5), (7) and they would like to avoid adverse events but most of them are "not afraid of" the adverse events (14), (2), (4), (5), (7). 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 (8).	

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 would probably favor the comparison, i.e. no post-discharge anticoagulation. The panel also considered that the certainty of the evidence was very low, and that the randomized controlled trial included patients who were at higher risk of VTE and lower risk of major bleeding than the total population of interest for this question.

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 drug prices (US) are listed.** **<u>Prophylactic-intensity anticoagulation</u>** Apixaban 2.5 mg po BID $520.71 Betrixaban 80 mg $472.65 Dabigatran 75 mg $240.41 Dalteparin 5,000 U $1,326.91 Enoxaparin 40 mg $176.75 Fondaparinux 2.5 mg/0.5 ml $313.20 Heparin SQ 5,000 U BID $34.91 Rivaroxaban 10 mg $508.72 **<u>Therapeutic-intensity anticoagulation</u>** Apixaban 5 mg po BID $533.01 Dabigatran 75, 110 or 150 mg BID $458.65 Dalteparin 15,000 U $3,767.54 Enoxaparin 80 mg BID $326.73 Fondaparinux 7.5mg/0.6 ml $466.73 Fondaparinux 10mg/0.8 ml $857.39 Heparin SQ 20,000 U BID $190.00 Rivaroxaban 20 mg $520.72 Warfarin INR 2.0 - 3.0 $4.96 (only drug cost - monitoring not included) https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html (Feb 17, 2022) http://www.goodrx.com/ and https://www.drugs.com/price-guide/ (Feb 17, 2022)	

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		

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 direct cost-effectiveness analyses in post-discharge COVID-19 patients were identified. **Evidence on extended VTE prophylaxis in discharged medical and surgical patients without COVID-19 based on our 2018 review for the ASH clinical practice guidelines on VTE:** Thirteen studies reported the comparison of extended (typically 30-35 days) with short course (typically 10-14 days) prophylaxis strategies of the same medication (Bergqvist 1999, Bergqvist 2000, Bischof 2006, Cain 2012, Dahl 2003, Davies 2000, Detournay 1998, Dranitsaris 2009, Haentjens 2004, Sarasin 1996, Sarasin 2002, Skedgel 2007, Uppal 2012), while four other studies compared extended prophylaxis with another medication (the comparisons included extended fondaparinux with enoxaparin, extended enoxaparin compared with warfarin, and extended rivaroxaban compared with enoxaparin) (Capri 2010, Duran 2011, Dahl 2003, Friedman 2000). In general, extended prophylaxis was cost effective compared with short-course prophylaxis across different settings, except in one study that suggested ten days of dalteparin was cost-effective compared to extended prophylaxis, and another that suggested the marginal cost of extended prophylaxis with LMWH was too expensive. In patients at high bleeding risk, extended prophylaxis was found to generate higher costs.	The panel agreed that the identified cost-effectiveness evidence was too indirect for this population and intervention. The evidence was mentioned, but the panel judgement was "no included studies" for the question of interest.

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 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. People who are not insured may have less access to post-discharge anticoagulation. If a recommendation to not use anticoagulants is made then equity would be increased. This judgement also considered potential cost for the intervention, in particular for those paying out of pocket.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Indirect evidence on VTE treatment in outpatients based on a 2018 review:** Observational studies suggest patients with acute proximal DVT treated at home with daily LMWH injections had greater treatment satisfaction than the hospital care group receiving 5 days of LMWH and VKA at the hospital. Even returning to the hospital every day for LMWH injections was considered more convenient than being admitted. Almost all patients in an outpatient treatment program were satisfied with this treatment. (Hull et al., 2009) (Zed et al., 2008) VTE patient satisfaction with DOACs was reported to be higher and treatment burden lower than with LMWH/VKA. (Attaya et al., 2012) Observational studies also reported that the proportion of patients with VTE managed at home varies substantially between countries and settings, with most physicians preferring to treat patients with VTE at home if feasible. (Schwarz et al., 2001)(Spencer et al., 2009)(Stein et al., 2010)(Blattler et al., 2005)(Squizzato et al., 2010)	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. However, the panel acknowledged that given the very low certainty in evidence, there may be regional variation in acceptability of the intervention.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Indirect evidence on VTE treatment in outpatients based on our 2018 review:** Observational research suggests the following regarding feasibility issues to utilizing home treatment with anticoagulation for VTE patients: One study comparing an emergency department care model to a decentralized primary and home care model for management of acute lower-extremity DVT found that the decentralized model was feasible and easily implemented by primary care providers and the two models were shown to have comparable short-term outcomes with respect to effectiveness and safety. (Vinson 2006) A retrospective cohort study of 175 patients found that higher-risk patients with acute PE sent home within 24 hours of emergency-department registration more commonly received expedited follow up within three days than low-risk patients. For all patients, the rate of adverse outcomes at 5 days and 30 days was very low, though the study was not adequately powered to measure safety of the management approach. (Vinson 2015) Interventions including a VTE care pathway and systematic education, patient follow-up, order sets and post-hospital care, might improve duration of hospital stay, prevent re-admissions and reduce cost of care. (Misky et al., 2014)	The intervention was felt to be feasible as prophylactic anticoagulation is already being used in the management of some patients after hospitalization for COVID-19.

SUMMARY OF JUDGEMENTS

CRITERIA	ADOLOPMENT	IMPORTANCE FOR DECISION
PROBLEM	Yes	
DESIRABLE EFFECTS	Trivial	
UNDESIRABLE EFFECTS	Trivial	
CERTAINTY OF EVIDENCE	Very low	
VALUES	Possibly important uncertainty or variability	
BALANCE OF EFFECTS	Probably favors the comparison	
RESOURCES REQUIRED	Large costs	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies	
COST EFFECTIVENESS	No included studies	
EQUITY	Reduced	
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 against using outpatient anticoagulant thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital and 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:

- An individualized assessment of the patient's risk of thrombosis and bleeding and shared decision-making is important when deciding whether to use post-discharge thromboprophylaxis.
- The panel acknowledged that post-discharge thromboprophylaxis may be reasonable in patients judged to be at high thrombotic risk and low bleeding risk.

Justification

Overall justification

Although the panel judged the overall certainty of evidence to be very low for both desirable and undesirable effects, the panel judged that the trivial benefits would not outweigh the trivial harms of post-discharge anticoagulation. The panel therefore suggested against outpatient anticoagulant thromboprophylaxis in COVID-19 patients, while acknowledging that individualized decision-making is required. This recommendation will continue to be updated based on a living review of evolving evidence.

Detailed justification

Balance of effects

While there was a suggestion of a trivial reduction in all-cause mortality, PE, and DVT with post-discharge anticoagulation, this evidence was of very low certainty. There was less uncertainty in the potential undesirable effects of anticoagulation increasing the risk of major bleeding. Moreover, the panel considered that there was higher quality indirect evidence from non-COVID-19 critically ill patients for an increase in the risk of major bleeding with post-discharge anticoagulation, although the magnitude of this effect was uncertain in the COVID-19 population. The panel however acknowledged the potential for benefit and noted that an individualized decision is important for each patient based on an assessment of thrombotic and bleeding risk.

Subgroup considerations

No subgroup considerations.

Implementation considerations

Risk-assessment models to estimate thrombotic risk in hospitalized patients (critically or non-critically ill) 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 post-discharge anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding risk.

References:

1. Spyropoulos AC, Cohen SL, Gianos E, et al. Validation of the IMPROVE-DD risk assessment model for venous thromboembolism among hospitalized patients with COVID-19. *Res Pract Thromb Haemost.* 2021 Feb 24:5(2):296-300.

2. Goldin M, Lin SK, Kohn N, et al. External validation of the IMPROVE-DD risk assessment model for venous thromboembolism among inpatients with COVID-19. *J Thromb Thrombolysis.* 2021 Nov5;52(4):1032-1035.

3. Paz Rios LH, Minga I, Kwak E, et al. Prognostic value of venous thromboembolism risk assessment models in patients with severe COVID-19. *TH Open.* 2021 Jun 22;5(2):e211-e219.

Monitoring and evaluation

As there is currently a conditional recommendation against post-discharge anticoagulation, monitoring should focus on use based on patients' thrombotic and bleeding risk profiles. If patients do receive post-discharge prophylaxis, they should be monitored for any bleeding related complications.

Research priorities

· Additional large, high-quality randomized controlled trials to increase the certainty of the evidence on health effects

· Studies assessing baseline VTE risk, major bleeding risk, and mortality in COVID-19 patients being discharged from hospital

· 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

· Further development and validation of risk assessment models for thrombosis and bleeding in COVID-19 patients being discharged from hospital

· Studies examining the impact of anticoagulant therapy on thrombosis and bleeding outcomes in patients of differing race/ethnicity

· Studies estimating the relative disutility of thrombotic and bleeding outcomes in COVID-19 patients being discharged from hospital

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