QUESTION

Should prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux, Aspirin, Clopidogrel, Prasugrel, Ticagrelor vs. no anticoagulation/antiplatelets be used for patients with COVID-19 who are being discharged from the hospital who do not have suspected or confirmed VTE and who do not have another indication for antithrombotic therapy?

POPULATION:	patients with COVID-19 who are being discharged from the hospital who do not have suspected or confirmed VTE and who do not have another indication for antithrombotic therapy
INTERVENTION:	prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux, Aspirin, Clopidogrel, Prasugrel, Ticagrelor
COMPARISON:	no anticoagulation/antiplatelets
MAIN OUTCOMES:	Mortality; Pulmonary Embolism; Deep Venous Thrombosis; Venous Thromboembolism; Major Bleeding; Ischemic Stroke; ST-elevation Myocardial Infarction; Readmission
SETTING:	Inpatient
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 April 2021, COVID-19 has affected more than 138 million people. While many infected individuals remain asymptomatic, others develop severe illness requiring acute inpatient or outpatient care.** Patients with COVID-19 related acute or 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. Early reports have suggested that hospitalized medical (non-surgical) patients with COVID-19 related acute or critical illness may have improved clinical outcomes with anticoagulant prophylaxis. However, the optimal duration of anticoagulation and extended use of prophylaxis after hospital discharge and its effect on clinical outcomes remains 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	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		The panel remarked that the absolute effects for mortality may be overestimated, in particular after considering the indirect evidence from hospitalized medical patients with and without COVID-19 (see ASH VTE guidelines on hospitalized medical patients and ASH VTE guidelines on acutely ill hospitalized COVID-19 medical patients).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no anticoagulation/antiplatelets	Risk difference with prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux, Aspirin

Mortality - Anticoagulation follow up: 30 days	4906 (1 observational study)[a]	⨁◯◯◯ VERY LOW[b,c]	**OR 0.55** (0.37 to 0.83)	Median		
				11 per 1,000[d]	**5 fewer per 1,000** (7 fewer to 2 fewer)	
Pulmonary Embolism - Anticoagulation follow up: 30 days	5353 (2 observational studies)[e]	⨁◯◯◯ VERY LOW[f]	**OR 0.76** (0.46 to 1.25)	Median		
				6 per 1,000[d]	**1 fewer per 1,000** (3 fewer to 1 more)	
Deep Venous Thrombosis - Anticoagulation follow up: 30 days	5353 (2 observational studies)[e]	⨁◯◯◯ VERY LOW[c]	**OR 0.76** (0.46 to 1.25)	Median		
				2 per 1,000[d]	**0 fewer per 1,000** (1 fewer to 0 fewer)	
Venous Thromboembolism - Anticoagulation assessed with: PE or DVT follow up: 30 days	5353 (2 observational studies)[e]	⨁◯◯◯ VERY LOW[f]	**OR 0.76** (0.46 to 1.25)	Median		
				17 per 1,000[d]	**4 fewer per 1,000** (9 fewer to 4 more)	
Major Bleeding - Anticoagulation follow up: 30 days	4906 (1 observational study)[a]	⨁◯◯◯ VERY LOW[g]	**OR 1.52** (0.86 to 2.67)	Median		
				1 per 1,000[d]	**1 more per 1,000** (0 fewer to 2 more)	
NON-COVID acutely ill - Major Bleeding -	27794 (4 RCTs)	⨁⨁◯◯ LOW[h]	**RR 2.09** (1.33 to 3.27)	Low		
				4 per 1,000	**4 more per 1,000**	

Anticoagulation					(1 more to 9 more)
				High	
				12 per 1,000[i]	**13 more per 1,000** (4 more to 27 more)
Ischemic Stroke - Anticoagulation follow up: 30 days	5353 (2 observational studies)[e]	⨁◯◯◯ VERY LOW[f]	**OR 0.76** (0.46 to 1.25)	Median	
				2 per 1,000[d]	**0 fewer per 1,000** (1 fewer to 0 fewer)
ST-elevation Myocardial Infarction - Anticoagulation assessed with: Myocardial Infarction follow up: 30 days	5353 (2 observational studies)[e]	⨁◯◯◯ VERY LOW[f]	**OR 0.76** (0.46 to 1.25)	Median	
				2 per 1,000[d]	**0 fewer per 1,000** (1 fewer to 0 fewer)
Readmission - Anticoagulation timing of exposure: 30 days	61 cases 61 controls (1 observational study)[j]	⨁◯◯◯ VERY LOW[k,l]	**OR 0.92** (0.41 to 2.05)	Median	
				61 per 1,000[d]	**5 fewer per 1,000** (35 fewer to 57 more)

a. Giannis 2021
b. Effect estimate for composite outcome of mortality, venous thrombosis, and arterial thrombosis
c. Adjusted effect estimate, but 39% of discharged patients without follow-up data. Characteristics of patients lost to follow-up comparable with those included
d. Median among eligible studies
e. Eswaran 2021 & Giannis 2021
f. Eswaran 2021 only corrected for age and ICU admission, residual confounding likely; Giannis 2021 reported adjusted effect estimate, but 39% of discharged

patients without follow-up data. Characteristics of patients lost to follow-up comparable with those included

g. Unadjusted effect estimate, and 39% of discharged patients without follow-up data. Characteristics of patients lost to follow-up comparable with those included
h. Very serious indirectness. Evidence from non-COVID-19 patients; Indirect comparison of interventions although no different effects observed in sensitivity analysis
i. 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
j. Parra 2020
k. There is a clinically important difference between the smallest and largest possible effect of prophylactic intensity antithrombotic therapy, lowering the certainty by one level for imprecision
l. Small case-control study only matched for age, gender and time period

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/antiplatelets	Risk difference with prophylactic-intensity DOACs, LMWH, UFH, Fondaparinux, Aspirin
Mortality - Anticoagulation follow up: 30 days	4906 (1 observational study)[a]	⨁◯◯◯ VERY LOW[b,c]	**OR 0.55** (0.37 to 0.83)	Median	
				11 per 1,000[d]	**5 fewer per 1,000** (7 fewer to 2 fewer)

ADDITIONAL CONSIDERATIONS

Pulmonary Embolism - Anticoagulation follow up: 30 days	5353 (2 observational studies)[e]	⨁◯◯◯ VERY LOW[f]	**OR 0.76** (0.46 to 1.25)	Median		
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Major Bleeding - Anticoagulation follow up: 30 days	4906 (1 observational study)[a]	⨁◯◯◯ VERY LOW[g]	**OR 1.52** (0.86 to 2.67)	Median		
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NON-COVID acutely ill - Major Bleeding - Anticoagulation	27794 (4 RCTs)	⨁⨁◯◯ LOW[h]	**RR 2.09** (1.33 to 3.27)	Low		
				4 per 1,000	**4 more per 1,000** (1 more to 9 more)	
				High		
				12 per 1,000[i]	**13 more per 1,000**	

					(4 more to 27 more)
Ischemic Stroke - Anticoagulation follow up: 30 days	5353 (2 observational studies)[e]	⨁◯◯◯ VERY LOW[f]	**OR 0.76** (0.46 to 1.25)	Median	
				2 per 1,000[d]	**0 fewer per 1,000** (1 fewer to 0 fewer)
ST-elevation Myocardial Infarction - Anticoagulation assessed with: Myocardial Infarction follow up: 30 days	5353 (2 observational studies)[e]	⨁◯◯◯ VERY LOW[f]	**OR 0.76** (0.46 to 1.25)	Median	
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	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 j. Parra 2020 k. There is a clinically important difference between the smallest and largest possible effect of prophylactic intensity antithrombotic therapy, lowering the certainty by one level for imprecision l. Small case-control study only matched for age, gender and time period	

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		Given the evidence in the evidence profile, the panel agreed that the overall certainty was very low across critical outcomes.

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	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.

	trade off) (3), (1) - survey of ASH panelists: 0.44) **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 discussed the trade off for benefits and harms, and some members suggested that the indirect evidence about major bleeding provides more than very low certainty and therefore made the choice for probably favours the comparison (no anticoagulation or antiplatelet agents).

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 $466.2	

	Enoxaparin 30 mg $191.74 Dalteparin 5,000 U $1,222.81 Dabigatran 75 mg $222.41 Heparin SQ 5,000 U BID $32.47 Fondaparinux 2.5 mg/0.5 ml $40.37 (Medicaid) $319.54 Rivaroxaban 10 mg $471.95 https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html (Sep 09, 2020) http://www.goodrx.com/ and https://www.drugs.com/price-guide/ (Sep 09, 2020)	

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	**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.	People who are not insured may have less access to post-discharge antithrombotic therapy. 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) **Indirect evidence on VTE prophylaxis in medical (non-surgical) patients** based on our 2018 review: One study describing barriers associated with utilizing prophylaxis reported that among 1,894 patients with acutely ill medical conditions from 29 Canadian hospitals, 23% received some type 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 factor, and duration of hospitalization; however, use of prophylaxis was unacceptably low in all groups. (Kahn 2007) 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, where as 54% of physicians expected patients to miss one injection in a month of therapy. (Cimminiello 2012) 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. (Lloyd 2012) 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. (Pendergraft 2013)	

	A survey of 453 hospital physicians (61% internal medicine specialty) presented four clinical case scenarios, with results reflecting a substantial heterogeneity in the clinical management of medical patients at risk for VTE. In one scenario, prolonged prophylaxis in the post-acute setting was voted for by more than 80% of participants, in contrast to recommendations from current guidelines; replies to the other three clinical scenarios on dosing or choice of anticoagulant were more heterogeneous with none of the options selected by more than 60% of participants. (Dentali 2014)	

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) **Indirect evidence on VTE prophylaxis in medical patients** based on our 2018 review: One study describing barriers to utilizing prophylaxis reported on a survey among ICU directors, bedside pharmacists, thromboprophylaxis research coordinators and physician site investigators in 27 Canadian ICU's, showing 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 pre-printed orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. Acceptability of facilitators varied across ICU's. (Cook 2014) A systematic review of RCTs aimed at increasing the use of prophylaxis or appropriate prophylaxis in hospitalized adult patients found increased prescription of prophylaxis associated with alerts and	

	multifaceted interventions, and increased prescription of appropriate prophylaxis associated with alerts. (Kahn 2018)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	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
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	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**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

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 not using anticoagulant outpatient 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. Validated risk assessment models to estimate thrombotic and bleeding risk in COVID-19 patients following hospital discharge are not available. The panel

acknowledged that post-discharge thromboprophylaxis may be reasonable in patients judged to be at high thrombotic risk and low bleeding risk.

Justification

The panel judged both the benefits and harms to be trivial based on the absolute effects. The certainty of the evidence is very low although higher for the harms based on ample indirect evidence of increased major bleeding with antithrombotic therapy.

This recommendation will be updated based on a living review of evolving evidence.

Detailed justification

Balance of effects

While there was a suggestion of a trivial mortality benefit and reduction in VTE with post-discharge antithrombotic therapy, this evidence was of very low certainty. There was less uncertainty in the potential undesirable effects of antithrombotic therapy increasing the risk of major bleeding complications. 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

Risk assessment models for assessing thrombosis and bleeding risk in non-COVID-19 hospitalized patients have been developed. However, these tools have not been validated in patients hospitalized with COVID-19 or for those discharged after COVID-19.

Implementation considerations

Given that no anticoagulation or antiplatet agents are recommended, implementation should not be a concern as long as it is not common practice in some settings already.

Monitoring and evaluation

As there is currently a conditional recommendation against post-discharge prophylaxis, there are no monitoring or implementation considerations. If patients do receive post-discharge prophylaxis, they should be monitored for any bleeding related complications.

Research priorities

RCT evidence is required in order to increase the certainty in the estimates.

The panel emphasized that there is an urgent need for more high-quality prospective studies and randomized controlled trials examining the effect of post-discharge antithrombotic therapy.

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. 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.
3. 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.
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. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.