QUESTION

Should DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at intermediate-intensity vs. Prophylactic intensity be used for Patients with COVID-19 related critical illness who do not have suspected or confirmed VTE (PICO 1a)?	
POPULATION:	Patients with COVID-19 related critical illness who do not have suspected or confirmed VTE (PICO 1a)
INTERVENTION:	DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at intermediate-intensity
COMPARISON:	Prophylactic intensity
MAIN OUTCOMES:	Mortality; Pulmonary embolism; Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT); Venous thromboembolism; Major bleeding; Renal replacement therapy; Ischemic stroke; Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization; (ST-elevation) myocardial infarction;
SETTING:	Inpatient
PERSPECTIVE:	Population
BACKGROUND:	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.
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, Davila, Diuguid, Griffin, Kahn, Klok, Lee, Mustafa, Neumann, A. Pai, Righini, Sanfilippo, Schünemann, Siegal, Skara, Touri, Tseng. **Panel members recused as a result of risk of conflict of interest:** DeSancho

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 137 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.	The panel prioritized this question through question rating and discussions given the high perceived burden of thromboembolic disease or complications in COVID-19 patients. The benefits and harms of different intensity anticoagulation for preventive purposes are unclear.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Original	
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	This research evidence describes what is currently known based on studies describing the baseline risk of events and direct evidence of treatment effects (September 16, 2020). When no information is provided, it indicates that there is no direct evidence yet (that is, in COVID-19 patients). *See Appendix 1*	The panel agreed that there was a moderate benefit with the intervention, with a reduction in mortality and VTE as desirable effects. There was no direct evidence available on the effects of the intervention and comparison on the following outcomes, which were also identified as priorities by the panel: Multiple Organ Failure; Ischemic stroke (severe); Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization (duration); and ST-elevation myocardial infarction.
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● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	*See Appendix 1*	The panel agreed that there was trivial benefit with the intervention with respect to reduction in PE, VTE, and length of ICU stay as desirable effects.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Original	
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	This research evidence describes what is currently known based on studies describing the baseline risk of events and direct evidence of treatment effects (September 16, 2020). When no information is provided, it indicates that there is no direct evidence yet (that is, in COVID-19 patients). *See Appendix 1*	There was consensus among the panel that there was moderate harm with the intervention, with an increase in major bleeding as an undesirable effect. There was no direct evidence available on the effects of the intervention and comparison on the following outcomes, which were also identified as priorities by the panel: Multiple Organ Failure; Ischemic stroke (severe); Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization (duration); and ST-elevation myocardial infarction.
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○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	*See Appendix 1*	The panel agreed that there was small harm with the intervention with respect to an increase in major bleeding as an undesirable effect.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Original	

● Very low ○ Low ○ Moderate ○ High ○ No included studies	All critical outcomes were rated as very low certainty evidence.	There was consensus among the panel that the certainty of evidence for desirable and undesirable effects was very low. However, there was less uncertainty regarding the impact of the intervention on undesirable effects (major bleeding) than on desirable effects (mortality, VTE), as the panel also considered a plethora of indirect evidence in non-COVID-19 critically ill patients demonstrating a dose-dependent effect on bleeding risk. The magnitude of this effect was uncertain in the COVID-19 critically ill population.
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○ Very low ● Low ○ Moderate ○ High ○ No included studies	Example: 'no additional research evidence, local or global considered': or 'additional local evidence indentified: xxx'; and/or 'additional global evidence indentified: xxx'. The evidence of effects came from a randomized controlled trial, but due to very serious imprecision in the estimates for most critical outcomes the overall certainty of the evidence was judged to be Low.	There was consensus among the panel that the certainty of evidence for desirable and undesirable effects was 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 (Etxeandia-Ikobaltzeta et al., 2020) 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.	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.

	The relative importance of the outcomes* was as follows in the identified studies: **Pulmonary embolism: 0.63-0.93** (Hogg et al., 2013), (Hogg et al., 2014), (Locadia et al., 2004) - survey of ASH panelists: 0.25 for severe to 0.62 for mild) **Deep vein thrombosis: 0.64-0.99** (Hogg et al., 2013), (Hogg et al., 2014), (Marvig et al., 2015), (Utne et al., 2016) - 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)** (Locadia et al., 2004) **Major bleeding as indicated by gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)** (Hogg et al., 2013), (Locadia et al., 2004) - survey of ASH panelists: 0.44) **Muscular bleeding: 0.76 (time trade off)** (Locadia et al., 2004) **Minor intracranial bleeding event: 0.75 (standard gamble)** (Hogg et al., 2013) **Major intracranial bleeding event: 0.15 (standard gamble)** (Hogg et al., 2013) **Central nervous system bleeding: 0.29-0.60 (standard gamble)** (Lenert et al., 1997), (O'Meara et al., 1994) **Treatment with LMWH: 0.993 (time trade off)** (Marchetti et al., 2001) * 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 (Haac et al., 2016), (Locadia et al., 2004), (Quante et al., 2012), (Wong et al., 2015) and that they would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona et al., 2000), (Haac et al., 2016), (O'Meara et al., 1994), (Quante et al., 2012), (Wong et al., 2015). 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 (Maxwell et al., 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Original	
○ 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		Although the panel judged the certainty of evidence to be very low for both desirable and undesirable effects, the panel also considered indirect evidence in non-COVID-19 critically ill patients supporting a dose-dependent increase in major bleeding with anticoagulation. The panel judged that there was less uncertainty in the impact of the intervention on undesirable effects (major bleeding) than on desirable effects (mortality, VTE).

	Update April 2021	
○ 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 trivial desirable effects on reduction in PE, VTE, and ICU length of stay with the intervention were outweighed by a small increase in major bleeding as harms.

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 anticoagulation</u>** **Apixaban 2.5 mg po BID $466.20** **Betrixaban 80 mg $452.28** **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** **<u>Therapeutic anticoagulation</u>** **Apixaban 5 mg po BID $472.81** **Dalteparin 15,000 U $3,530.52** **Dabigatran 75, 110 or 150 mg BID $442.94** **Enoxaparin 120 mg $262.40** **Fondaparinux 7.5mg/0.6 ml US$ 67.75 (Medicaid) $745.69** **Fondaparinux 10mg/0.8 ml US$ 67.75 (Medicaid) $915.64** **Heparin IV (40 units/mL, cost per 500 mL x 24) $261.14** **Rivaroxaban 20 mg $500.12** **Warfarin INR 2.0 - 3.0 $8.47 (only drug cost - monitoring not included)** 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)	This comparison focused on differences in drug costs between prophylactic-intensity versus intermediate-intensity or therapeutic-intensity anticoagulation. While the total drug cost of the intervention would be higher, this was felt to be negligible in comparison to the total costs of providing critical care to these patients. It was noted that the costs of certain anticoagulants may vary geographically.

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.	

Cost effectiveness

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

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

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Original	
○ 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 African Americans and Hispanics. However, the intervention was not felt to have a differential impact on health equity relative to the comparison.
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○ 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 African Americans 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 doses of pharmacological prophylaxis: **With regards to different anticoagulants, we previously identified the following research that related to acceptability.** Studies and surveys suggest the following regarding barriers associated with the intervention and its use across anticoagulants based on our 2018 review: A survey among 568 physicians and 825 patients from 5 countries showed that more patients considered injectable treatments effective than considered oral treatments effective (87% versus 76%, respectively). This trend was well predicted by the physicians (98% and 61%, respectively). Additionally, 46% of patients would accept an injectable treatment program lasting >2 months (67% for life-threatening diseases), a figure underestimated by physicians (11% and 46%, respectively). Overall, 73% of patients stated they would never miss an injection, whereas 54% of physicians expected patients to miss one injection in a month of therapy. (Cimminiello et al., 2012) 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. (Fanikos et al., 2010) 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 et al., 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 et al., 2013) 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. (Panju et al., 2011) Among 64 medical patients, 59% received appropriate VTE prophylaxis using LMWH. (Eijgenraam et al., 2015)	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 low certainty in evidence, there may be regional variation in acceptability of the intervention, particularly in regions where the 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	Feasibilty of using higher versus lower doses of anticoagulants. **Feasibility and use of any pharmacological prophylaxis in other populations:** Studies showed the following barriers to utilizing the intervention/option: Among 1,894 patients 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. (Kahn, 2007) 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. (Cook et al., 2014)	The intervention was felt to be feasible as differing intensities of anticoagulation are already used broadly in the management of critically ill patients without COVID-19.

SUMMARY OF JUDGEMENTS

CRITERIA	ORIGINAL	IMPORTANCE FOR DECISION	UPDATE APRIL 2021	IMPORTANCE FOR DECISION
PROBLEM	Yes		The same as original	
DESIRABLE EFFECTS	Moderate		Trivial	
UNDESIRABLE EFFECTS	Moderate		Small	
CERTAINTY OF EVIDENCE	Very low		Low	
VALUES	Possibly important uncertainty or variability		The same as original	
BALANCE OF EFFECTS	Probably favors the comparison		Probably favors the comparison	
RESOURCES REQUIRED	Negligible costs and savings		The same as original	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies		The same as original	
COST EFFECTIVENESS	No included studies		The same as original	
EQUITY			Probably no impact	
ACCEPTABILITY	Probably yes		The same as original	
FEASIBILITY	Yes		The same as original	

TYPE OF RECOMMENDATION

Original

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
○	●	○	○	○

Update April 2021

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

Original

Recommendation

The American Society of Hematology (ASH) guideline panel *suggests* using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with coronavirus disease 2019 (COVID-19)–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE)

Remark:

- Between the time this recommendation was published online (27 October 2020) and when it was published in *Blood Advances*, a press release (https://www-nih-gov.libaccess.lib.mcmaster.ca/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation for patients with COVID-19–related critical illness. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients.
- Patients with COVID-19–related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit (ICU). Examples include patients requiring hemodynamic support, ventilatory support, and renal-replacement therapy.
- 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 and bleeding risk in hospitalized patients are available, but they have not been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding risk.
- At present, there is no direct high-certainty evidence comparing different types of anticoagulants. The selection of a specific agent (eg, low-molecular-weight heparin, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing personal protective equipment (PPE) use or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).
- This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation (ECMO) or continuous renal-replacement therapy (CRRT).

Justification

Overall justification

Although the panel judged the certainty of evidence to be very low for both desirable and undesirable effects, the panel considered the plethora of indirect evidence supporting a dose-dependent increase in major bleeding reported with anticoagulation. Hence, the panel agreed that there was less uncertainty regarding the increase in undesirable effects (bleeding) compared with the influence on desirable effects (i.e., reduction in mortality and VTE) reported with intermediate-intensity or therapeutic-intensity anticoagulation. Without compelling evidence for benefit, the usual practice of prophylactic-intensity anticoagulation in critically ill medical patients without COVID-19 was suggested while acknowledging that individualized decision-making is required. This recommendation will be updated based on a living review of evolving evidence.

Detailed justification

Balance of effects

While there was a suggestion of mortality benefit and reduction in VTE with intermediate-intensity or therapeutic-intensity anticoagulation, this evidence was of very low certainty. There was less uncertainty in the potential undesirable effects of intermediate-intensity or therapeutic-intensity anticoagulation in 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 a dose-dependent increase in the risk of major bleeding with anticoagulation, although the magnitude of this effect was uncertain in the COVID-19 population. Given that there was very low certainty for benefit to offset the moderate risk of major bleeding complications, the usual practice of prophylactic-intensity anticoagulation in critically ill non-COVID-19 patients was suggested. 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. The panel emphasized that there is an urgent need for more high-quality prospective studies and randomized controlled trials examining the effect of differing anticoagulation intensities.

Update April 2021

Recommendation

The American Society of Hematology (ASH) guideline panel *suggests* using prophylactic-intensity over intermediate-intensity anticoagulation for patients with coronavirus disease 2019 (COVID-19)–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE) (low certainty of evidence).

Remark:

- The ASH guideline panel plans to continue to update this recommendation when the full results of other trials become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients.
- **A now expired recommendation published on October 27, 2020compared therapeutic-intensity or intermediate-intensity with prophylactic-intensity anticoagulation in patients with COVID-19-related critical illness. With the emergence of new evidence, this recommendation has now been split into two recommendations: a recommendation comparing intermediate-intensity vs. prophylactic-intensity anticoagulation (Recommendation 1a) and a separate recommendation comparing therapeutic-intensity vs. prophylactic-intensity anticoagulation (Recommendation 1b).**
- Patients with COVID-19–related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit (ICU). Examples include patients requiring hemodynamic support, ventilatory support, and renal-replacement therapy.

- 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 and bleeding risk in hospitalized patients are available, but they have not been validated for patients with COVID-19. The panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding risk.
- At present, there is no direct high-certainty evidence comparing different types of anticoagulants. The selection of a specific agent (eg, low-molecular-weight heparin, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing personal protective equipment (PPE) use or staff exposure to COVID-19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).
- This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation (ECMO) or continuous renal-replacement therapy (CRRT).

Justification

Overall justification

The panel judged the certainty of evidence to be low for both desirable and undesirable effects. The trivial benefits of the intervention with respect to reduction in PE, VTE, and length of ICU stay were judged to be outweighed by a small increase in major bleeding. Without compelling evidence for benefit, the usual practice of prophylactic-intensity anticoagulation in critically ill patients without COVID-19 was suggested while acknowledging that individualized decision-making is required.

Detailed justification

Balance of effects

There was a suggestion of a trivial benefit with reduction in PE, VTE, and ICU length of stay with intermediate-intensity anticoagulation, but this evidence was of low certainty. Moreover, a small harm in major bleeding was observed which was judged to outweigh these trivial benefits. While the evidence for harm was also of low certainty in COVID-19 specific studies, the panel also considered that there was higher quality indirect evidence from non-COVID-19 critically ill patients for a dose-dependent increase in the risk of major bleeding with anticoagulation. Given that there was low certainty evidence for benefit to offset the small risk of major bleeding complications, the usual practice of prophylactic-intensity anticoagulation in critically ill patients was suggested. The panel however acknowledged that an individualized decision is important for each patient, based on an assessment of thrombotic and bleeding risk.

Subgroup considerations

For patients with extremes of body weight or renal impairment, dose adjustment of prophylactic-intensity anticoagulation may be appropriate.

Implementation 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.

References:
1. Barbar S, Noventa F, Rossetto V, et al. A risk assssment 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 critically 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 critically ill patients receiving anticoagulation therapy.

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Research priorities

- Studies assessing baseline VTE risk in critically ill patients on prophylactic-intensity anticoagulation therapy
- Randomized controlled trials comparing anticoagulation at differing intensities (prophylactic vs. intermediate vs. therapeutic)
- Studies examining the impact of non-anticoagulant interventions (e.g., anti-complement therapy, corticosteroids, antiviral therapies, anticytokine therapies, antiplatelet therapies, monoclonal antibody therapy, convalescent plasma) on thrombotic risk
- Development or validation of risk assessment models for thrombosis and bleeding in patients with COVID-19 related critical illness
- Studies examining the impacts 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

APPENDICES

Appendix 1

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
Mortality follow up: mean 30 days	562 (1 RCT)[1,a,b]	⨁⨁⨁◯ MODERATE[c,d]	**OR 1.09** (0.78 to 1.53)[e]	Study population	
				409 per 1,000	**21 more per 1,000** (58 fewer to 105 more)
				Mean across studies	
				236 per 1,000[1,2,3,4,f]	**16 more per 1,000** (42 fewer to 85 more)
Pulmonary embolism follow up: range 14 days to 20 days	562 (1 RCT)[5,b,g]	⨁⨁◯◯ LOW[c,d,h]	**OR 0.41** (0.08 to 2.13)[i]	Study population	
				17 per 1,000	**10 fewer per 1,000** (16 fewer to 19 more)
				Mean across studies	
				98 per 1,000[3,4,6,j]	**55 fewer per 1,000** (89 fewer to 90 more)
Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) follow up: range 14 days to 20 days[b]	562 (1 RCT)[7,k]	⨁⨁◯◯ LOW[c,l]	**OR 0.74** (0.23 to 2.35)[m]	Study population	
				24 per 1,000	**6 fewer per 1,000** (19 fewer to 31 more)
				Mean across studies	
				106 per 1,000[3,4,n]	**25 fewer per 1,000** (79 fewer to 112 more)

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
Venous thromboembolism assessed with: DVT or PE follow up: mean 30 days[b]	562 (1 RCT)[8,9,o]	⨁⨁◯◯ LOW[c,d]	**OR 0.93** (0.37 to 2.32)[p]	Study population	
				35 per 1,000	**2 fewer per 1,000** (22 fewer to 43 more)
				Mean across studies	
				130 per 1,000[10,3,6,q]	**8 fewer per 1,000** (78 fewer to 127 more)
Major bleeding follow up: mean 16 days[b]	562 (1 RCT)[1,a]	⨁⨁◯◯ LOW[c,d]	**OR 1.83** (0.53 to 5.93)[r]	Study population	
				14 per 1,000	**11 more per 1,000** (7 fewer to 64 more)
				Mean across studies	
				84 per 1,000[1,s]	**60 more per 1,000** (38 fewer to 268 more)
Multiple Organ Failure assessed with: Requirement for Renal replacement therapy follow up: mean 14 days	0 (0 studies)[t]	-	not estimable	Mean across studies	
				125 per 1,000[4,u]	**125 fewer per 1,000** (125 fewer to 125 fewer)
Ischemic stroke assessed with: any ischemic stroke follow up: mean 30 days	562 (1 RCT)[t]	⨁⨁◯◯ LOW	**OR 1.03** (0.06 to 16.65)	Study population	
				3 per 1,000	**0 fewer per 1,000** (3 fewer to 52 more)
				Mean across studies	

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
				34 per 1,000[4,6,v]	**1 more per 1,000** (32 fewer to 335 more)
Intracranial hemorrhage	562 (1 RCT)[1,w]	⨁⨁◯◯ LOW[c,d]	**OR 3.12** (0.13 to 76.91)[x]	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Invasive ventilation assessed with: ventilator free days Scale from: 0 to 30 follow up: mean 30 days	60 (1 RCT)[t]	⨁⨁⨁◯ MODERATE	-	The mean invasive ventilation was **0** days	MD **0 days** (0 to 0)
Limb amputation	0 (0 studies)[t]	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
ICU hospitalization assessed with: length of stay	11 (1 RCT)[t]	⨁⨁⨁◯ MODERATE	-	The mean ICU hospitalization was **0** days	MD **1 days fewer** (4 fewer to 3 more)
(ST-elevation) myocardial infarction follow up: mean 30 days	562 (1 RCT)[t]	⨁⨁◯◯ LOW	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Mean across studies	
				21 per 1,000[6,y]	**21 fewer per 1,000** (21 fewer to 21 fewer)
				Study population	

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
Renal replacement therapy follow up: mean 30 days	562 (1 RCT)	⨁⨁◯◯ LOW	**OR 1.49** (0.58 to 3.86)	24 per 1,000	**12 more per 1,000** (10 fewer to 64 more)
				Moderate	
				125 per 1,000	**51 more per 1,000** (48 fewer to 230 more)

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a. Ferguson et al. 2020. Therapeutic versus Prophylactic anticoagulation intensity. Relative effect estimate adjusted for adjuvant therapy. Intervention group: Therapeutic anticoagulation was administered as either a continuous infusion of heparin dose-adjusted based on unfractionated heparin levels (UFH), or by subcutaneous 1 mg/kg twice daily or 1.5 mg/kg daily low molecular weight heparin (LMWH). LMWH dose adjustments were made based on anti-Xa levels in the event of renal insufficiency. Patients who were receiving oral anticoagulation prior to admission and remaining on anticoagulation were included in the therapeutic anticoagulation group. Control group: All patients in the control group received DVT chemoprophylaxis in the form of enoxaparin 40 mg subcutaneously daily, enoxaparin 30 mg twice daily, enoxaparin 0.5 mg/kg twice daily, or heparin 5,000 units subcutaneously two or three times daily.
b. Length of follow-up based on studies informing about baseline risk
c. Very small number of events and patients included in the intervention studies, lowering the certainty by two levels for imprecision
d. Selection bias, residual confounding, and other risk of bias lowering certainty in the non-randomized studies
e. Adjusted relative effect estimate of Therapeutic versus Prophylactic anticoagulation intensity. Unadjusted studies (Llitjos 2020 and Ferguson 2020) showed a OR (pooled) of 0.89 (0.43-1.84)

f. Pooled average across four baseline risk studies
g. Taccone et al. 2020. Intermediate versus Prophylactic anticoagulation intensity. Relative effect estimate adjusted for: age, immunosuppressive agents, hypertension, obesity, D-dimers on admission, Wells score, time from admission to CT-scan, C-reactive protein on the day of CTPA and use of prone positioning. Other variables, such as D-Dimers on the day of CTPA, tidal volume or volume ventilation on the day of CTPA, were not included because considered as the result of EP (i.e. thrombus formation and dead space)
h. Large effect upgrading does not apply because only one imprecise study was available
i. Adjusted relative effect estimate for Intermediate anticoagulation intensity (n=18) versus 'others' (Prophylactic anticoagulation intensity n=22, Not on anticoagulation n=42)
j. We have not listed the baseline risk of 35.3% observed in one of the studies and a risk of 4.2% in another study as they likely present random high and low values and we listed the pooled average across three studies
k. Trigonis et al. 2020. Intermediate versus Prophylactic anticoagulation intensity
l. High risk of bias as relative effect estimate is not adjusted for potential confounders
m. Unadjusted relative effect estimate for Intermediate versus Prophylactic anticoagulation intensity
n. Pooled estimate of two studies with likely random low (0.5%) and high (27.5%) baseline risk estimates
o. Fraisse et al. 2020, Llitjos et al. 2020. Therapeutic versus Prophylactic anticoagulation intensity
p. The average relative effect estimates of two unadjusted studies (Llitjos 2020 and Fraisse 2020) showed a OR (pooled) of 0.87 (0.45-1.67)
q. Pooled average across three baseline risk studies
r. Unadjusted relative effect estimate for Therapeutic versus Prophylactic anticoagulation intensity
s. Baseline risk estimate from Ferguson et al. 2020
t. No studies identified measuring this outcome for the comparison of different anticoagulation intensities in COVID-19 patients. No relative and absolute effects could be calculated
u. Baseline risk estimate for renal replacement therapy from Klok et al. 2020
v. Pooled baseline risk from two studies
w. Ferguson et al. 2020. Therapeutic versus Prophylactic anticoagulation intensity
x. No intracranial hemorrhages in Prophylactic intensity group (baseline risk), and 1 intracranial hemorrhage in Therapeutic intensity group
y. Baseline risk from Lodigiani et al. 2020

a.