QUESTION

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

	recommendation): Angchaisuksiri, Blair, Cuker, Dane, Diuguid, Griffin, Klok, Lee, Mustafa, Neumann, A. Pai, Righini, Sanfilippo, Schünemann, Siegal, Skara, Terrell, Touri, Tseng. Two panel members (DeSancho, Kahn) were recused.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**As of September 2021, COVID-19 has affected more than 225 million people. While many infected individuals remain asymptomatic, others develop severe illness requiring acute inpatient or outpatient care.** Patients with COVID-19 related acute illness may develop hemostatic abnormalities and hypercoagulability. Early studies demonstrated high rates of venous thrombotic complications. Furthermore, COVID-19 may be associated with arterial thrombotic complications and microvascular thrombosis, particularly in the lungs. Early reports have suggested that hospitalized medical patients with COVID-19 related acute illness may have improved clinical outcomes with anticoagulant prophylaxis. However, the optimal intensity of anticoagulation and its effect on clinical outcomes remains uncertain and there is substantial variation in clinical practice. References: 1. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18:2103-2109. 2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844-847. 3. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147. 4. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46:1089-1098. 5. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild Covid-19 infection. *J Thromb Haemost*. 2020;18:2031-2033. 6. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120-128. 7. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18:1094-1099. 8. Rosovsky RP, Sanfilippo KM, Wang TF, et al. Anticoagulation Practice Patterns in COVID-19: A Global	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.

Survey. Res Pract Thromb Haemost. 2020;4(6): 969-983.

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 Prophylactic-intensity	Risk difference with DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Therapeutic-intensity
All-cause mortality follow-up: range 5 days to 50 days[a]	3298 (3 RCTs)[1,2,3]	⨁◯◯◯ Very low[b,c,d]	**OR 0.79** (0.37 to 1.68)[e,f]	Low	
				72 per 1,000[g,h]	**14 fewer per 1,000** (44 fewer to 43 more)
				Moderate	
				99 per 1,000[i,g]	**19 fewer per 1,000** (60 fewer to 57 more)
				High	
				134 per 1,000[g,j]	**25 fewer per 1,000** (80 fewer to 72 more)

ADDITIONAL CONSIDERATIONS

The panel rated the desirable effects of the intervention to be small, primarily driven by a reduction in pulmonary embolism (PE). PE in COVID-19 patients is often subsegmental and in these situations may be less consequential for the patient.(1, 2, 3)

Pulmonary embolism follow-up: range 4 days to 34 days[a]	3305 (3 RCTs)[1,2,3]	⨁⨁◯◯ Low[k,l]	**OR 0.46** (0.26 to 0.81)[m]	Low		
				17 per 1,000[h,n]	**9 fewer per 1,000** (13 fewer to 3 fewer)	
				Moderate		
				30 per 1,000[i,n]	**16 fewer per 1,000** (22 fewer to 6 fewer)	
				High		
				53 per 1,000[j,n]	**28 fewer per 1,000** (39 fewer to 10 fewer)	
Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) follow-up: range 5 days to 34 days[a]	3305 (3 RCTs)[1,2,3]	⨁⨁◯◯ Low[l,o]	**OR 0.81** (0.37 to 1.75)[p]	Low		
				5 per 1,000[h,q]	**1 fewer per 1,000** (3 fewer to 4 more)	
				Moderate		
				9 per 1,000[i,q]	**2 fewer per 1,000** (6 fewer to 7 more)	
				High		
				15 per 1,000[j,q]	**3 fewer per 1,000** (9 fewer to 11 more)	
Venous thromboembolism follow-up: range 5	1079 (2 RCTs)[1,3]	⨁⨁◯◯ Low[l,o]	**OR 0.51** (0.26 to 1.02)[r]	Low		
				22 per	**11 fewer per 1,000** (16 fewer to 0	

days to 34 days[a]				1,000[h,s]	fewer)
				Moderate	
				36 per 1,000[i,s]	**17 fewer per 1,000** (26 fewer to 1 more)
				High	
				59 per 1,000[j,s]	**28 fewer per 1,000** (43 fewer to 1 more)
Multiple organ failure follow-up: mean 30 days[a]	465 (1 RCT)[3]	⨁◯◯◯ Very low[t,u]	**OR 0.09** (0.01 to 1.68)	Low	
				51 per 1,000[h,v]	**46 fewer per 1,000** (50 fewer to 32 more)
				Moderate	
				72 per 1,000[i,v]	**65 fewer per 1,000** (71 fewer to 43 more)
				High	
				102 per 1,000[j,v]	**92 fewer per 1,000** (101 fewer to 58 more)
Ischemic stroke (severe) assessed with: any stroke follow-up: range 5	3305 (3 RCTs)[1,2,3]	⨁⨁◯◯ Low[d,w]	**OR 0.88** (0.13 to 5.99)[x]	Low	
				1 per 1,000[h,y]	**0 fewer per 1,000** (1 fewer to 5 more)

days to 30 days[a]				Moderate	
				4 per 1,000[i,y]	**0 fewer per 1,000** (3 fewer to 19 more)
				High	
				11 per 1,000[j,y]	**1 fewer per 1,000** (10 fewer to 51 more)
Invasive mechanical ventilation follow-up: range 7 days to 30 days[a]	465 (1 RCT)[3]	⨁⨁◯◯ Low[c]	**OR 0.70** (0.32 to 1.54)[z]	Low	
				18 per 1,000[h,aa]	**5 fewer per 1,000** (12 fewer to 9 more)
				Moderate	
				48 per 1,000[i,aa]	**14 fewer per 1,000** (32 fewer to 24 more)
				High	
				124 per 1,000[j,aa]	**34 fewer per 1,000** (81 fewer to 55 more)
Limb amputation assessed with: Major adverse limb event follow-up: mean 30 days[bb]	614 (1 RCT)[1]	⨁◯◯◯ Very low[w,cc]	**OR 0.33** (0.01 to 8.03)	Study population	
				3 per 1,000	**2 fewer per 1,000** (3 fewer to 23 more)
ICU hospitalization	465	⨁⨁◯◯	**OR 0.79**	Low	

follow-up: range 3 days to 28 days[a]	(1 RCT)[3]	Low[c]	(0.48 to 1.29)	39 per 1,000[h,dd]	**8 fewer per 1,000** (20 fewer to 11 more)
				Moderate	
				78 per 1,000[j,dd]	**15 fewer per 1,000** (39 fewer to 20 more)
				High	
				149 per 1,000[j,dd]	**27 fewer per 1,000** (71 fewer to 35 more)
ST-elevation myocardial infarction assessed with: Any myocardial infarction follow-up: range 5 days to 30 days[a]	3305 (3 RCTs)[1,2,3]	⨁⨁◯◯ Low[ee]	**OR 0.96** (0.17 to 5.54)[ff]	Low	
				1 per 1,000[h,gg]	**0 fewer per 1,000** (1 fewer to 5 more)
				Moderate	
				5 per 1,000[j,gg]	**0 fewer per 1,000** (4 fewer to 22 more)
				High	
				18 per 1,000[j,gg]	**1 fewer per 1,000** (15 fewer to 74 more)

1. Lopes, Renato D., de Barros e Silva, Pedro Gabriel Melo, Furtado, Remo H. M., Macedo, Ariane Vieira Scarlatelli, Bronhara, Bruna, Damiani, Lucas Petri, Barbosa, Lilian Mazza, de Aveiro Morata, Júlia, Ramacciotti, Eduardo, de Aquino Martins, Priscilla, de Oliveira, Aryadne Lyrio, Nunes, Vinicius Santana, Ritt, Luiz Eduardo Fonteles, Rocha, Ana Thereza, Tramujas, Lucas, Santos, Sueli V., Diaz, Dario Rafael Abregu, Viana, Lorena Souza, Melro, Lívia Maria Garcia, de Alcântara Chaud, Mariana Silveira,

	Figueiredo, Estêvão Lanna, Neuenschwander, Fernando Carvalho, Dracoulakis, Marianna Deway Andrade, Lima, Rodolfo Godinho Souza Dourado, de Souza Dantas, Vicente Cés, Fernandes, Anne Cristine Silva, Gebara, Otávio Celso Eluf, Hernandes, Mauro Esteves, Queiroz, Diego Aparecido Rios, Veiga, Viviane C., Canesin, Manoel Fernandes, de Faria, Leonardo Meira, Feitosa-Filho, Gilson Soares, Gazzana, Marcelo Basso, Liporace, Idelzuíta Leandro, de Oliveira Twardowsky, Aline, Maia, Lilia Nigro, Machado, Flávia Ribeiro, de Matos Soeiro, Alexandre, Conceição-Souza, Germano Emílio, Armaganijan, Luciana, Guimarães, Patrícia O., Rosa, Regis G., Azevedo, Luciano C. P., Alexander, John H., Avezum, Alvaro, Cavalcanti, Alexandre B., Berwanger, Otavio. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. The Lancet; 2021. 2. The ATTACC ACTIV-4a and REMAP-CAP Investigators, . Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. New England Journal of Medicine; 2021. 3. Sholzberg, M., Tang, G. H., Rahhal, H., AlHamzah, M., Kreuziger, L. B., Ni Ainle, F., Alomran, F., Alayed, K., Alsheef, M., AlSumait, F., Pompilio, C. E., Sperlich, C., Tangri, S., Tang, T., Jaksa, P., Suryanarayan, D., Almarshoodi, M., Castellucci, L., James, P. D., Lillicrap, D., Carrier, M., Beckett, A., Colovos, C., Jayakar, J., Arsenault, M. P., Wu, C., Doyon, K., Andreou, E. R., Dounaevskaia, V., Tseng, E. K., Lim, G., Fralick, M., Middeldorp, S., Lee, A. Y. Y., Zuo, F., da Costa, B. R., Thorpe, K. E., Negri, E. M., Cushman, M., Juni, P., investigators, Rapid,Trial. Heparin for Moderately Ill Patients with Covid-19. medRxiv; Jul 12 2021. a. Follow up durations from the observational studies informing the baseline risk b. Heterogeneity in meta-analysis: I squared value 80%, Chi-square p-value for heterogeneity 0.006; substantially different point estimates and non-overlapping 95% CI's c. The 95% CI of the absolute effect includes both considerable harm and considerable benefit d. Although the ATTACC/ACTIV-4/REMAP-CAP trial used response-adaptive randomization that led to some loss in prognostic balance between the groups, the panel decided not to rate down the certainty for risk of bias as the pooled absolute effect estimate was already rated down for serious inconsistency and very serious imprecision e. Combining the adjusted OR from the ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial (aOR = 0.83; 95% credible interval 0.59-1.15) with the unadjusted OR's from Lopes 2021 (OR = 1.55; 95% CI 0.89-2.69) and Sholzberg 2021 (OR = 0.22; 95% CI 0.07-0.65) resulted in a pooled OR that was comparable (OR = 0.76; 95% CI 0.35-1.65) f. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.80 (95% CI: 0.46-1.36) g. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Al-Samkari 2020, Arachchillage 2021, Artifoni 2020, Boari 2020, Campochiaro 2020, Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Fortini 2020, Ierardi 2021, Kevorkian 2021, Martinelli 2021, Paolisso 2020, Pesavento 2020, Piazza 2020, Russo 2020, Santoliquido 2020, Soni 2020 h. Lower bound of the 95% CI for the pooled mean event rate among	

	baseline risk studies i. Pooled mean event rate among baseline risk studies j. Upper bound of the 95% CI for the pooled mean event rate among baseline risk studies k. The 95% CI of the absolute effect includes both considerable benefit and negligible benefit l. Patients and caregivers were unblinded during the trials, and it was unknown if there were important differences in how often diagnostic imaging tests were performed, and how often they were positive. Certainty was rated down for serious risk of bias m. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.44 (95% CI: 0.26-0.73) n. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Arachchillage 2021, Artifoni 2020, Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Louhaichi 2020, Middeldorp 2020, Moll 2020, Pancani 2020, Pesavento 2020, Piazza 2020, Russo 2020 o. The pooled analysis included few events, and the 95% CI of the absolute effect included both benefit and harm p. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.54 (95% CI: 0.30-0.98) q. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Arachchillage 2021,Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Moll 2020, Pancani 2020, Pesavento 2020, Piazza 2020, Russo 2020 r. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.51 (95% CI: 0.26-1.02) s. Baseline risks were calculated using the control group risks from the two RCTs and the following observational studies: Al-Samkari 2020, Arachchillage 2021,Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Mei 2020, Moll 2020, Pesavento 2020, Russo 2020 t. Outcome in trial was multi-system organ failure as cause of death u. The 95% CI of the absolute effect includes both considerable harm and considerable benefit; effect estimate based on a total of 5 events from 1 trial v. Baseline risks were calculated using the control group risks from the RCT and the following observational studies: Arachchillage 2021, Piazza 2020 w. Baseline risk and effect estimate based on a total of 1 event x. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.90 (95% CI: 0.19-4.39) y. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Arachchillage 2021, Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Piazza 2020 z. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.74 (95% CI: 0.44-1.25) aa. Baseline risks were calculated using the control group risks from the RCT and the following observational studies: Artifoni 2020, Campochiaro 2020, Kevorkian 2021, Martinelli 2021, Paolisso 2020, Piazza 2020 bb. Follow-up duration for Lopes 2021, from which the baseline risk and effect	

estimate were used

cc. The ACTION trial reported on major adverse limb events, which was considered a surrogate outcome for limb amputation.

dd. Baseline risks were calculated using the control group risks from the RCT and the following observational studies: Arachchillage 2021, Artifoni 2020, Campochiaro 2020, Fortini 2020, Jimenez-Guiu 2020, Paolisso 2020, Pesavento 2020

ee. The 95% CI of the absolute effect includes both important harm and negligible benefit; effect estimate calculated based on a total of 4 events

ff. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 0.58 (95% CI: 0.13-2.61)

gg. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Piazza 2020

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

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

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Prophylactic-intensity	Risk difference with DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at Therapeutic-intensity
Major bleeding follow-up: range 5 days to 30 days[a]	3306 (3 RCTs)[1,2,3]	⨁⨁◯◯ Low[b,c]	**OR 1.80** (0.87 to 3.75)[d,e]	Low	
				7 per 1,000[f,g]	**6 more per 1,000** (1 fewer to 19 more)
				Moderate	
				13 per 1,000[h,f]	**10 more per 1,000** (2 fewer to 34 more)

ADDITIONAL CONSIDERATIONS

The panel rated the undesirable effects of the intervention to be small, primarily driven by an increase in major bleeding.

There was uncertainty regarding the severity of major bleeding events. Some panelists felt that the majority of major bleeding events in this population were likely to be of lower severity (category 1-2),(4, 5) although such data were not consistently reported in the included studies. Other panelists voiced concern regarding the potentially significant morbidity and high case-fatality associated with anticoagulant-associated major bleeding.(6, 7)

				High	
				23 per 1,000[f,i]	**18 more per 1,000** (3 fewer to 58 more)
Intracranial hemorrhage follow-up: range 5 days to 30 days[a]	3305 (3 RCTs)[1,2,3]	⨁⨁◯◯ Low[j,k]	**OR 2.95** (0.12 to 72.74)	Low	
				0 per 1,000[g,l]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[h,l]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				10 per 1,000[i,l]	**19 more per 1,000** (9 fewer to 414 more)

1. Lopes, Renato D., de Barros e Silva, Pedro Gabriel Melo, Furtado, Remo H. M., Macedo, Ariane Vieira Scarlatelli, Bronhara, Bruna, Damiani, Lucas Petri, Barbosa, Lilian Mazza, de Aveiro Morata, Júlia, Ramacciotti, Eduardo, de Aquino Martins, Priscilla, de Oliveira, Aryadne Lyrio, Nunes, Vinicius Santana, Ritt, Luiz Eduardo Fonteles, Rocha, Ana Thereza, Tramujas, Lucas, Santos, Sueli V., Diaz, Dario Rafael Abregu, Viana, Lorena Souza, Melro, Lívia Maria Garcia, de Alcântara Chaud, Mariana Silveira, Figueiredo, Estêvão Lanna, Neuenschwander, Fernando Carvalho, Dracoulakis, Marianna Deway Andrade, Lima, Rodolfo Godinho Souza Dourado, de Souza Dantas, Vicente Cés, Fernandes, Anne Cristine Silva, Gebara, Otávio Celso Eluf, Hernandes, Mauro Esteves, Queiroz, Diego Aparecido Rios, Veiga, Viviane C., Canesin, Manoel Fernandes, de Faria, Leonardo Meira, Feitosa-Filho, Gilson Soares, Gazzana, Marcelo Basso, Liporace, Idelzuíta Leandro, de Oliveira Twardowsky, Aline, Maia, Lilia Nigro, Machado, Flávia Ribeiro, de Matos Soeiro, Alexandre, Conceição-Souza, Germano Emílio, Armaganijan, Luciana, Guimarães, Patrícia O., Rosa, Regis G., Azevedo, Luciano C. P., Alexander, John H., Avezum, Alvaro, Cavalcanti, Alexandre B., Berwanger, Otavio. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. The Lancet; 2021.
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	3. Sholzberg, M., Tang, G. H., Rahhal, H., AlHamzah, M., Kreuziger, L. B., Ni Ainle, F., Alomran, F., Alayed, K., Alsheef, M., AlSumait, F., Pompilio, C. E., Sperlich, C., Tangri, S., Tang, T., Jaksa, P., Suryanarayan, D., Almarshoodi, M., Castellucci, L., James, P. D., Lillicrap, D., Carrier, M., Beckett, A., Colovos, C., Jayakar, J., Arsenault, M. P., Wu, C., Doyon, K., Andreou, E. R., Dounaevskaia, V., Tseng, E. K., Lim, G., Fralick, M., Middeldorp, S., Lee, A. Y. Y., Zuo, F., da Costa, B. R., Thorpe, K. E., Negri, E. M., Cushman, M., Juni, P., investigators, Rapid,Trial. Heparin for Moderately Ill Patients with Covid-19. medRxiv; Jul 12 2021. a. Follow up durations from the observational studies informing the baseline risk b. The 95% CI of the absolute effect includes both considerable harm and negligible benefit c. Although the ATTACC/ACTIV-4/REMAP-CAP trial used response-adaptive randomization that led to some loss in prognostic balance between the groups, the panel decided not to rate down the certainty for risk of bias as the pooled absolute effect estimate was already rated down for very serious imprecision d. Combining the adjusted OR from the ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial (aOR = 1.80; 95% credible interval 0.90-3.74) with the unadjusted OR's from Lopes 2021 (OR = 2.50; 95% CI 0.78-8.04) and Sholzberg 2021 (OR = 0.52; 95% CI 0.09-2.84) resulted in a comparable pooled effect (OR = 1.65; 95% CI 0.87-3.16) e. Adding the HEP-COVID 2021 trial results from a published conference presentation in sensitivity analysis resulted in a pooled OR of 1.79 (95% CI: 1.00-3.21) f. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Al-Samkari 2020, Arachchillage 2021, Dutch COVID & Thrombosis Coalition 2021 (1st and 2nd wave), Fujiwara 2021, Moll 2020, Pancani 2020, Paolisso 2020, Pesavento 2020, Russo 2020 g. Lower bound of the 95% CI for the pooled mean event rate among baseline risk studies h. Pooled mean event rate among baseline risk studies i. Upper bound of the 95% CI for the pooled mean event rate among baseline risk studies j. Baseline risk and effect estimate based on a total of 1 event k. Although the ATTACC/ACTIV-4/REMAP-CAP trial used response-adaptive randomization that led to some loss in prognostic balance between the groups, the panel decided not to rate down the certainty for risk of bias as the pooled absolute effect estimate was already rated down for serious inconsistency and very serious imprecision l. Baseline risks were calculated using the control group risks from the three RCTs and the following observational studies: Al-Samkari 2020, Pesavento 2020	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	Overall certainty is based on the lowest certainty of any critical outcome according to GRADE.	Certainty of the evidence for Major Bleeding was considered somewhat higher than for other outcomes based on direct evidence (in COVID patients) and indirect evidence (from non-COVID patients) (low certainty). There was a reduction in pulmonary embolism with the intervention, which was also low certainty. The reduction in mortality was considered very low certainty based on serious inconsistency and very serious imprecision.

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 (18) suggests that affected people place a moderate relative value on avoiding pulmonary embolism, DVT, major bleeding and a low relative value (indicating great impairment on outcomes such as intracranial bleeds). There is moderate to high certainty in these findings. The evidence suggests that there is variability around these values or relative importance that the affected population places on these outcomes but this may be a result of the way they are measured. Below is the research evidence as synthesized. Survey results with ASH VTE guideline panels using visual analogue scales showed lower values than the one described below and this is explained by the fact that methods such as the standard gamble produce results that suggest less impairment of health. **The relative importance of the outcomes* was as follows in the identified studies:** **Pulmonary embolism: 0.63-0.93 (moderate certainty)** (9), (19), (8) - survey of ASH panelists: 0.25 for severe to 0.62 for mild) **Deep vein thrombosis: 0.64-0.99 (moderate certainty)** (9), (19), (8),(20), (21) - survey of ASH panelists: 0.43 for severe to 0.71 for mild) **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off) (moderate certainty) (8) **Major bleeding as indicated by gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off) (moderate certainty) ((9, 8)) - survey of ASH panelists: 0.44) **Muscular bleeding:** 0.76 (time trade off) (moderate certainty) (8) **Minor intracranial bleeding event:** 0.75 (standard gamble) (high certainty) (9) **Major intracranial bleeding event:** 0.15 (standard gamble) (high certainty) (9)	Panel members noted that there was possible uncertainty and variability in the relative value patients place on avoiding major bleeding events compared with reducing thrombotic events. One patient representative on the panel reported that he would potentially place a higher value on avoiding bleeding than on preventing a VTE event.

	Central nervous system bleeding: 0.29-0.60 (standard gamble) (very low certainty) (10, 11) **Treatment with LMWH:** 0.993 (time trade off) (low certainty) (12)* 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 (13, 8, 14, 15) and that they would like to avoid adverse events but most of them are "not afraid of" the adverse events (16, 13, 11, 14, 15). 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 (17).	

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		Although the panel judged both the desirable and undesirable effects of the intervention to be small, it noted that there was somewhat greater certainty in the evidence for one of the key undesirable effects (major bleeding) based on both direct evidence in COVID patients, and on a substantial body of indirect evidence about bleeding risk in acutely ill non-COVID patients. At the same time, the reduction in mortality noted with the intervention was judged to be very uncertain based on serious inconsistency and very serious imprecision. The panel also noted that, although there may be variability in the relative value that patients place on various outcomes, on average, the disutility of a major bleed is greater than the disutility of PE. This may be particularly true in patients with COVID-19 related acute illness, in whom PE is often subsegmental and therefore of less potential clinical consequence. For these reasons, the panel judged that the balance of effects probably favors the comparison.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

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

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	These are listed drug prices for US resale. There should be little variation to these prices in the US.	Add considerations made be the adoloping panel, including the justification for any change in judgment.

Cost effectiveness

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

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

Equity

What would be the impact on health equity?

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

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Acceptability and use of higher versus lower intensity of pharmacological prophylaxis: **With regards to different anticoagulants, we previously identified the following research that related to acceptability.** Studies and surveys suggest the following regarding barriers associated with the intervention and its use across anticoagulants based on our 2018 review: A survey among 568 physicians and 825 patients from 5 countries showed that more patients considered injectable treatments effective than considered oral treatments effective (87% versus 76%, respectively). This trend was well predicted by the 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	The acceptability of the intervention to various stakeholders (patients, healthcare providers, institutions, etc.) was considered. The intervention was felt to be acceptable to patients. The intervention was felt to be acceptable to providers. The panel acknowledged that given the very low certainty in evidence, there may be regional variation in acceptability of the intervention, particularly in regions where hospitalization rates for COVID-19 and baseline VTE risk may differ (e.g., Asian populations).

	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)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Feasibility of using higher versus lower intensity of anticoagulants. **Feasibility and use of any pharmacological prophylaxis:** Studies showed the following barriers to utilizing the intervention/option: Among 1,894 acutely ill medical patients from 29 Canadian hospitals, 23% received some form of VTE prophylaxis, but only 16% received appropriate prophylaxis. Factors independently associated with greater use of prophylaxis included internist (vs. other specialty) as attending physician, university-associated (vs. community) hospital, immobilization, presence of >1 VTE risk factors, and duration of hospitalization, however, use of prophylaxis was unacceptably low in all groups. (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 acutely ill patients with COVID-19.(Rosovsky et al., 2020)

SUMMARY OF JUDGEMENTS

CRITERIA	JUDGEMENT
PROBLEM	Yes
DESIRABLE EFFECTS	Small
UNDESIRABLE EFFECTS	Small
CERTAINTY OF EVIDENCE	Very low
VALUES	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Probably favors the comparison
RESOURCES REQUIRED	Negligible costs and savings
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	No included studies
COST EFFECTIVENESS	No included studies
EQUITY	Probably no impact
ACCEPTABILITY	Probably yes
FEASIBILITY	Yes

TYPE OF RECOMMENDATION

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

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using prophylactic-intensity over therapeutic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects).

Remarks:

- Patients with COVID-19–related acute illness are defined as those with clinical features that would typically result in admission to a medicine inpatient ward without requirement for advanced clinical support. Examples include patients with dyspnea or mild to moderate hypoxia.
- An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity. Risk-assessment models to estimate thrombotic risk in hospitalized patients have been validated in COVID-19 patients, with modest prognostic performance. No risk assessment models for bleeding have been validated in COVID-19 patients. The panel acknowledges that 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 in patients with COVID-19. 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 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, etc.).

Justification

Overall justification

Although the panel judged the overall certainty of evidence to be very low, the panel considered the certainty of evidence to be somewhat higher for major bleeding, a key undesirable effect of the intervention. The panel also noted that, on average, patients may place greater value on avoiding major bleeding than avoiding a thromboembolic event, though they acknowledged the limitations of available evidence. Based on these judgments, the panel suggested prophylactic-intensity anticoagulation over therapeutic-intensity anticoagulation in acutely ill medical patients with COVID-19, while acknowledging that individualized decision-making is required. This recommendation will continue to be updated based on living reviews of evolving evidence.

Detailed justification

Balance of effects

The baseline risk of VTE in patients with COVID-19 related acute illness receiving prophylactic-intensity anticoagulation was relatively low, leading to fairly small absolute risk differences for patients receiving therapeutic-intensity compared to prophylactic-intensity anticoagulation. While there was a suggestion of a reduction in PE, invasive mechanical ventilation and ICU admission with therapeutic-intensity anticoagulation, this evidence was of low certainty. Moreover, the panel noted that PE in COVID-19 patients is often subsegmental, which is less consequential for patients than more proximal PE. The reduction in mortality with the intervention was considered very low certainty based on serious inconsistency and very serious imprecision. There was less uncertainty in the potential undesirable effects of therapeutic-intensity anticoagulation in increasing the risk of major bleeding. This was based on both direct evidence in COVID-19 patients and a substantial body of higher quality indirect evidence from non-COVID-19 acutely ill patients demonstrating a dose-dependent increase in the risk of major bleeding with anticoagulation. Moreover, the panel expressed concerns about the potential morbidity of anticoagulant-associated major bleeding events. Given that there was very low certainty for reduced mortality and a small absolute reduction in VTE to offset the small increase in risk of major bleeding complications with the intervention, the usual practice of prophylactic-intensity anticoagulation in acutely 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 randomized controlled trials examining the effect of differing anticoagulation intensities.

Subgroup considerations

For patients with extremes of body weight or renal impairment, dose adjustment of prophylactic-intensity anticoagulation may be appropriate. Assessment using the ICEMAN instrument indicated that the subgroup effect of DOAC (rivaroxaban) vs heparin (UFH or LMWH) had low to very low credibility (see manuscript appendix), and the overall effect is reported.

Implementation considerations

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

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Monitoring and evaluation

Patients receiving prophylactic-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 assessment for signs and symptoms of thromboembolism and bleeding are also necessary in acutely ill patients.

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

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Research priorities

- Large high-quality studies assessing baseline VTE risk, major bleeding risk, and mortality in acutely ill patients on prophylactic-intensity anticoagulation therapy
- Studies examining the impact of non-anticoagulant interventions (e.g., anti-complement therapy, corticosteroids, antiviral therapies, antiplatelet therapies, anticytokine therapies, monoclonal antibody therapies, convalescent plasma) on thrombotic risk
- Studies examining the impact of different viral variants on thrombotic risk
- Development and validation of risk assessment models with good prognostic performance for thrombosis and bleeding in patients with COVID-19 related acute 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
- Studies estimating the relative disutility of thrombotic and bleeding outcomes in patients with COVID-19 related acute illness

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