# QUESTION

## Should DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity vs. Prophylactic intensity be used for Patients with COVID-19 related critical illness who do not have suspected or confirmed VTE?

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| **POPULATION:** | Patients with COVID-19 related critical illness who do not have suspected or confirmed VTE |
| **INTERVENTION:** | DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity |
| **COMPARISON:** | Prophylactic intensity |
| **MAIN OUTCOMES:** | Mortality; Pulmonary embolism; Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT); Major bleeding; Multiple Organ Failure; Ischemic stroke (severe); Intracranial hemorrhage; Invasive mechanical ventilation; Limb amputation; ST-elevation myocardial infarction; Length of hospital admission; |
| **SETTING:** | Inpatient |
| **PERSPECTIVE:** | Population |
| **BACKGROUND:** | There is a high incidence of thrombotic complications in critically ill patients with COVID-19. In addition, these patients may develop a severe inflammatory response with endothelial dysfunction, which may lead to a hypercoagulable state. The extent to which hypercoagulability contributes to respiratory failure and multiorgan failure however remains unclear. The optimal intensity of anticoagulation and its effect on clinical outcomes is uncertain and is the focus of this evidence review<br><br>References:<br><br>1. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18:2103-2109.<br><br>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.<br><br>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.<br><br>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.<br><br>5. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost.* 2020 Sep 25;4(7):1178-1191. |
| **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, DeSancho, Diuguid, Griffin, Kahn, Klok, Lee, Mustafa, Neumann, 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 |
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| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes | **As of January 2022, COVID-19 has affected more than 330 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 | 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 |

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| ○ Varies<br>○ Don't know | 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.<br><br>Early reports have 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.<br><br>References:<br><br>1. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18:2103-2109.<br><br>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.<br><br>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.<br><br>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.<br><br>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.<br><br>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.<br><br>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. | harms of different intensity anticoagulation for preventive purposes are unclear. |

## Desirable Effects

How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
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| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | | The panel judged the desirable effects of therapeutic-intensity anticoagulation to be small based on the decision thresholds (see Appendix), primarily driven by a reduction in pulmonary embolism. |

| Outcomes | № of participants (studies) Follow-up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
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| | | | | Risk with Prophylactic intensity | Risk difference with DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at therapeutic-intensity |
| Pulmonary embolism follow-up: range 7 days to 30 days[a,b] | 1172 (2 RCTs)[1,2,c] | ⨁◯◯◯ Very low[d,e,f,g] | **OR 0.33** (0.18 to 0.60) | Low | |
| | | | | 40 per 1,000[h] | **26 fewer per 1,000** (33 fewer to 16 fewer) |
| | | | | Mean across studies | |
| | | | | 80 per 1,000[i] | **52 fewer per 1,000** (65 fewer to 30 fewer) |
| | | | | High | |
| | | | | 153 per 1,000[j] | **97 fewer per 1,000** (122 fewer to 55 fewer) |
| Deep Venous Thrombosis of the upper leg (Proximal lower extremity DVT) follow-up: range 7 days to 30 days[a,k] | 1172 (2 RCTs)[1,2,c] | ⨁◯◯◯ Very low[d,g,l] | **OR 0.86** (0.37 to 2.01) | Low | |
| | | | | 16 per 1,000[h] | **2 fewer per 1,000** (10 fewer to 16 more) |
| | | | | Mean across studies | |
| | | | | 40 per 1,000[i] | **5 fewer per 1,000** (25 fewer to 37 more) |
| | | | | High | |

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| | | | | 94 per 1,000[j] | **12 fewer per 1,000** (57 fewer to 79 more) |
| Ischemic stroke (severe) assessed with: any ischemic stroke follow-up: range 7 days to 30 days[m] | 1172 (2 RCTs)[1,2,c] | ⨁◯◯◯ Very low[d,g,n] | **OR 0.94** (0.36 to 2.45) | Low | |
| | | | | 6 per 1,000[h] | **0 fewer per 1,000** (4 fewer to 9 more) |
| | | | | Mean across studies | |
| | | | | 12 per 1,000[o] | **1 fewer per 1,000** (8 fewer to 17 more) |
| | | | | High | |
| | | | | 23 per 1,000 | **1 fewer per 1,000** (15 fewer to 32 more) |
| ST-elevation myocardial infarction assessed with: Any myocardial infarction follow-up: range 7 days to 30 days[a,p] | 1172 (2 RCTs)[1,2,c] | ⨁◯◯◯ Very low[d,g,n] | **OR 0.73** (0.28 to 1.94) | Low | |
| | | | | 0 per 1,000[h] | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| | | | | Mean across studies | |
| | | | | 3 per 1,000[i] | **1 fewer per 1,000** (2 fewer to 3 more) |
| | | | | High | |
| | | | | 33 per 1,000[j] | **9 fewer per 1,000** (24 fewer to 29 more) |

1. Spyropoulos, A. C., Goldin, M., Giannis, D., Diab, W., Wang, J., Khanijo, S., Mignatti, A., Gianos, E., Cohen, M., Sharifova, G., Lund, J. M., Tafur, A., Lewis, P. A., Cohoon, K. P., Rahman, H., Sison, C. P., Lesser, M. L., Ochani, K., Agrawal, N., Hsia, J., Anderson, V. E., Bonaca, M., Halperin, J. L., Weitz, J. I., Investigators, Hep-Covid. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-

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| | Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Intern Med; Dec 1 2021.<br>2. Investigators, Remap-Cap, Investigators, A.,CTIV-4a, Investigators, Attacc, Goligher, E. C., Bradbury, C. A., McVerry, B. J., Lawler, P. R., Berger, J. S., Gong, M. N., Carrier, M., Reynolds, H. R., Kumar, A., Turgeon, A. F., Kornblith, L. Z., Kahn, S. R., Marshall, J. C., Kim, K. S., Houston, B. L., Derde, L. P. G., Cushman, M., Tritschler, T., Angus, D. C., Godoy, L. C., McQuilten, Z., Kirwan, B. A., Farkouh, M. E., Brooks, M. M., Lewis, R. J., Berry, L. R., Lorenzi, E., Gordon, A. C., Ahuja, T., Al-Beidh, F., Annane, D., Arabi, Y. M., Aryal, D., Baumann Kreuziger, L., Beane, A., Bhimani, Z., Bihari, S., Billett, H. H., Bond, L., Bonten, M., Brunkhorst, F., Buxton, M., Buzgau, A., Castellucci, L. A., Chekuri, S., Chen, J. T., Cheng, A. C., Chkhikvadze, T., Coiffard, B., Contreras, A., Costantini, T. W., de Brouwer, S., Detry, M. A., Duggal, A., Dzavik, V., Effron, M. B., Eng, H. F., Escobedo, J., Estcourt, L. J., Everett, B. M., Fergusson, D. A., Fitzgerald, M., Fowler, R. A., Froess, J. D., Fu, Z., Galanaud, J. P., Galen, B. T., Gandotra, S., Girard, T. D., Goodman, A. L., Goossens, H., Green, C., Greenstein, Y. Y., Gross, P. L., Haniffa, R., Hegde, S. M., Hendrickson, C. M., Higgins, A. M., Hindenburg, A. A., Hope, A. A., Horowitz, J. M., Horvat, C. M., Huang, D. T., Hudock, K., Hunt, B. J., Husain, M., Hyzy, R. C., Jacobson, J. R., Jayakumar, D., Keller, N. M., Khan, A., Kim, Y., Kindzelski, A., King, A. J., Knudson, M. M., Kornblith, A. E., Kutcher, M. E., Laffan, M. A., Lamontagne, F., Le Gal, G., Leeper, C. M., Leifer, E. S., Lim, G., Gallego Lima, F., Linstrum, K., Litton, E., Lopez-Sendon, J., Lother, S. A., Marten, N., Saud Marinez, A., Martinez, M., Mateos Garcia, E., Mavromichalis, S., McAuley, D. F., McDonald, E. G., McGlothlin, A., McGuinness, S. P., Middeldorp, S., Montgomery, S. K., Mouncey, P. R., Murthy, S., Nair, G. B., Nair, R., Nichol, A. D., Nicolau, J. C., Nunez-Garcia, B., Park, J. J., Park, P. K., Parke, R. L., Parker, J. C., Parnia, S., Paul, J. D., Pompilio, M., Quigley, J. G., Rosenson, R. S., Rost, N. S., Rowan, K., Santos, F. O., Santos, M., Santos, M. O., Satterwhite, L., Saunders, C. T., Schreiber, J., Schutgens, R. E. G., Seymour, C. W., Siegal, D. M., Silva, D. G.,Jr., Singhal, A. B., Slutsky, A. S., Solvason, D., Stanworth, S. J., Turner, A. M., van Bentum-Puijk, W., van de Veerdonk, F. L., van Diepen, S., Vazquez-Grande, G., Wahid, L., Wareham, V., Widmer, R. J., Wilson, J. G., Yuriditsky, E., Zhong, Y., Berry, S. M., McArthur, C. J., Neal, M. D., Hochman, J. S., Webb, S. A., Zarychanski, R.. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med; Aug 26 2021.<br><br>a. Follow up durations from the observational studies informing the baseline risk<br>b. The decision thresholds for Pulmonary Embolism (Moderate severity) were: 27 per 1,000 for Trivial/Small; 53 per 1,000 for Small/Moderate; 103 per 1,000 for Moderate/Large<br>c. mpRCT 2021 & unpublished data HEP-COVID 2021<br>d. In the control group, only 61% of all HEP-COVID patients (ICU group unknown) and 40% of REMAP-CAP/ACTIV-4a/ATTACC were on prophylactic-intensity anticoagulation. As higher intensities according to local practice were allowed in their protocols, not rated down for risk of bias but rated down one level for indirectness | |

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| | e. Large effect upgrading does not apply because only one imprecise study was available<br>f. The 95% CI of the absolute effect estimate crosses one decision threshold and includes small benefit and moderate benefit; rated down 1 level for serious imprecision<br>g. 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<br>h. Lower bound of the 95% CI for the pooled mean event rate among baseline risk studies<br>i. Pooled mean event rate among baseline risk studies<br>j. Upper bound of the 95% CI for the pooled mean event rate among baseline risk studies<br>k. The decision thresholds for Proximal Deep Venous Thrombosis (Moderate severity) were: 37 per 1,000 for Trivial/Small; 73 per 1,000 for Small/Moderate; 142 per 1,000 for Moderate/Large<br>l. The 95% CI of the absolute effect estimate crosses one decision threshold and the effect estimate is based on few events; rated down 2 levels for very serious imprecision<br>m. The decision thresholds for Ischemic Stroke (severe) were: 18 per 1,000 for Trivial/Small; 36 per 1,000 for Small/Moderate; 69 per 1,000 for Moderate/Large<br>n. The effect estimate is based on few events; rated down 2 levels for very serious imprecision<br>o. Pooled baseline risk from two studies<br>p. The decision thresholds for ST-elevation Myocardial Infarction were: 23 per 1,000 for Trivial/Small; 44 per 1,000 for Small/Moderate; 86 per 1,000 for Moderate/Large | |

## Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Large<br>● Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>○ Don't know | | The panel agreed that there was overall a moderate harm with therapeutic-intensity anticoagulation, based on small-to-moderate harms for multiple critical outcomes according to the decision thresholds (see Appendix). |

| 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 |
| Mortality follow-up: range 7 days to 30 days[a,b] | 1181 (2 RCTs)[1,2,c] | ⨁◯◯◯ Very low[d,e] | **OR 1.06** (0.84 to 1.35)[f] | Low | |
| | | | | 189 per 1,000[g] | **9 more per 1,000** (25 fewer to 50 more) |
| | | | | Mean across studies | |
| | | | | 241 per 1,000[h] | **11 more per 1,000** (30 fewer to 59 more) |
| | | | | High | |
| | | | | 301 per 1,000[i] | **12 more per 1,000** (35 fewer to 67 more) |
| Major bleeding follow-up: range 7 days to 30 days[a,j] | 1174 (2 RCTs)[1,2,k] | ⨁◯◯◯ Very low[d,l] | **OR 1.95** (0.75 to 5.09)[m] | Low | |
| | | | | 17 per 1,000[g] | **16 more per 1,000** (4 fewer to 64 more) |
| | | | | Moderate | |
| | | | | 24 per 1,000[h] | **22 more per 1,000** (6 fewer to 87 more) |
| | | | | Mean across studies | |

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|---|---|---|---|---|---|
| | | | | 33 per 1,000[i] | **29 more per 1,000** (8 fewer to 115 more) |
| Multiple Organ Failure follow-up: 30 days[n] | 78 (1 RCT)[1,o] | ⨁◯◯◯ Very low[p,q] | **OR 2.68** (0.50 to 14.18) | Low | |
| | | | | 32 per 1,000[g] | **49 more per 1,000** (16 fewer to 287 more) |
| | | | | Mean across studies | |
| | | | | 79 per 1,000[h] | **108 more per 1,000** (38 fewer to 470 more) |
| | | | | High | |
| | | | | 184 per 1,000[i] | **193 more per 1,000** (83 fewer to 578 more) |
| Intracranial hemorrhage follow-up: 30 days[r] | 83 (1 RCT)[1,o] | ⨁◯◯◯ Very low[s,t] | not estimable | Low | |
| | | | | 0 per 1,000[g] | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| | | | | Mean across studies | |
| | | | | 2 per 1,000[h] | **2 fewer per 1,000** (2 fewer to 2 fewer) |
| | | | | High | |
| | | | | 15 per 1,000[i] | **15 fewer per 1,000** (15 fewer to 15 fewer) |
| | | | | Study population | |

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| Invasive mechanical ventilation follow-up: 30 days[u] | 73 (1 RCT)[1,o] | ⨁◯◯◯ Very low[v,w] | **OR 1.21** (0.41 to 3.51) | 229 per 1,000 | **35 more per 1,000** (120 fewer to 281 more) |
| Limb amputation assessed with: Major adverse limb event follow-up: 30 days[a,x] | 83 (1 RCT)[1,o] | ⨁◯◯◯ Very low[y,z] | **OR 4.43** (0.21 to 95.06) | Low | |
| | | | | 0 per 1,000[g] | **0 fewer per 1,000** (0 fewer to 0 fewer) |
| | | | | Moderate | |
| | | | | 3 per 1,000[h] | **10 more per 1,000** (2 fewer to 219 more) |
| | | | | High | |
| | | | | 21 per 1,000[i] | **66 more per 1,000** (17 fewer to 650 more) |
| Length of hospital admission | 83 (1 RCT)[1] | ⨁◯◯◯ Very low[s,aa] | - | The mean length of hospital admission was **0** days | MD **2 days more** (0.44 more to 3.56 more) |


1. Spyropoulos, A. C., Goldin, M., Giannis, D., Diab, W., Wang, J., Khanijo, S., Mignatti, A., Gianos, E., Cohen, M., Sharifova, G., Lund, J. M., Tafur, A., Lewis, P. A., Cohoon, K. P., Rahman, H., Sison, C. P., Lesser, M. L., Ochani, K., Agrawal, N., Hsia, J., Anderson, V. E., Bonaca, M., Halperin, J. L., Weitz, J. I., Investigators, Hep-Covid. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Intern Med; Dec 1 2021.
2. Investigators, Remap-Cap, Investigators, A.,CTIV-4a, Investigators, Attacc, Goligher, E. C., Bradbury, C. A., McVerry, B. J., Lawler, P. R., Berger, J. S., Gong, M. N., Carrier, M., Reynolds, H. R., Kumar, A., Turgeon, A. F., Kornblith, L. Z., Kahn, S. R., Marshall, J. C., Kim, K. S., Houston, B. L., Derde, L. P. G., Cushman, M., Tritschler, T., Angus, D. C., Godoy, L. C., McQuilten, Z., Kirwan, B. A., Farkouh, M. E., Brooks, M. M., Lewis, R. J., Berry, L. R., Lorenzi, E., Gordon, A. C., Ahuja, T., Al-

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| | Beidh, F., Annane, D., Arabi, Y. M., Aryal, D., Baumann Kreuziger, L., Beane, A., Bhimani, Z., Bihari, S., Billett, H. H., Bond, L., Bonten, M., Brunkhorst, F., Buxton, M., Buzgau, A., Castellucci, L. A., Chekuri, S., Chen, J. T., Cheng, A. C., Chkhikvadze, T., Coiffard, B., Contreras, A., Costantini, T. W., de Brouwer, S., Detry, M. A., Duggal, A., Dzavik, V., Effron, M. B., Eng, H. F., Escobedo, J., Estcourt, L. J., Everett, B. M., Fergusson, D. A., Fitzgerald, M., Fowler, R. A., Froess, J. D., Fu, Z., Galanaud, J. P., Galen, B. T., Gandotra, S., Girard, T. D., Goodman, A. L., Goossens, H., Green, C., Greenstein, Y. Y., Gross, P. L., Haniffa, R., Hegde, S. M., Hendrickson, C. M., Higgins, A. M., Hindenburg, A. A., Hope, A. A., Horowitz, J. M., Horvat, C. M., Huang, D. T., Hudock, K., Hunt, B. J., Husain, M., Hyzy, R. C., Jacobson, J. R., Jayakumar, D., Keller, N. M., Khan, A., Kim, Y., Kindzelski, A., King, A. J., Knudson, M. M., Kornblith, A. E., Kutcher, M. E., Laffan, M. A., Lamontagne, F., Le Gal, G., Leeper, C. M., Leifer, E. S., Lim, G., Gallego Lima, F., Linstrum, K., Litton, E., Lopez-Sendon, J., Lother, S. A., Marten, N., Saud Marinez, A., Martinez, M., Mateos Garcia, E., Mavromichalis, S., McAuley, D. F., McDonald, E. G., McGlothlin, A., McGuinness, S. P., Middeldorp, S., Montgomery, S. K., Mouncey, P. R., Murthy, S., Nair, G. B., Nair, R., Nichol, A. D., Nicolau, J. C., Nunez-Garcia, B., Park, J. J., Park, P. K., Parke, R. L., Parker, J. C., Parnia, S., Paul, J. D., Pompilio, M., Quigley, J. G., Rosenson, R. S., Rost, N. S., Rowan, K., Santos, F. O., Santos, M., Santos, M. O., Satterwhite, L., Saunders, C. T., Schreiber, J., Schutgens, R. E. G., Seymour, C. W., Siegal, D. M., Silva, D. G.,Jr., Singhal, A. B., Slutsky, A. S., Solvason, D., Stanworth, S. J., Turner, A. M., van Bentum-Puijk, W., van de Veerdonk, F. L., van Diepen, S., Vazquez-Grande, G., Wahid, L., Wareham, V., Widmer, R. J., Wilson, J. G., Yuriditsky, E., Zhong, Y., Berry, S. M., McArthur, C. J., Neal, M. D., Hochman, J. S., Webb, S. A., Zarychanski, R.. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med; Aug 26 2021.<br><br>a. Follow up durations from the observational studies informing the baseline risk<br>b. The decision thresholds for All-Cause Mortality were: 16 per 1,000 for Trivial/Small; 31 per 1,000 for Small/Moderate; 60 per 1,000 for Moderate/Large<br>c. mpRCT 2021 & unpublished data HEP-COVID 2021<br>d. In the control group, only 61% of all HEP-COVID patients (ICU group unknown) and 40% of REMAP-CAP/ACTIV-4a/ATTACC were on prophylactic-intensity anticoagulation. As higher intensities according to local practice were allowed in their protocols, not rated down for risk of bias but rated down one level for indirectness<br>e. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes moderate harm and small benefit; rated down 3 levels for very serious imprecision<br>f. Combining the adjusted OR from the mpRCT (aOR = 1.19; 95% credible interval 0.90-1.57 [reverse of reported aOR 0.84; 95% credible interval 0.64-1.11 for survival to discharge]) with the unadjusted OR from HEP-COVID resulted in a pooled OR that was comparable (OR = 1.16; 95% CI 0.89-1.50)<br>g. Lower bound of the 95% CI for the pooled mean event rate among baseline risk studies<br>h. Pooled mean event rate among baseline risk studies | |

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| | i. Upper bound of the 95% CI for the pooled mean event rate among baseline risk studies<br>j. The decision thresholds for Major Bleeding were: 23 per 1,000 for Trivial/Small; 46 per 1,000 for Small/Moderate; 89 per 1,000 for Moderate/Large<br>k. mpRCT 2021 & HEP-COVID 2021<br>l. The 95% CI of the absolute effect estimate crosses two decision thresholds and the effect estimate is based on few events; rated down 2 levels for very serious imprecision<br>m. Combining the adjusted OR from the mpRCT (aOR = 1.48; 95% credible interval 0.75-3.04) with the unadjusted OR from HEP-COVID resulted in a pooled OR that was comparable (OR = 1.90; 95% CI 0.58-6.22)<br>n. The decision thresholds for Multiple Organ Failure were: 18 per 1,000 for Trivial/Small; 36 per 1,000 for Small/Moderate; 70 per 1,000 for Moderate/Large<br>o. Unpublished data HEP-COVID 2021<br>p. Baseline risks based on renal replacement in the absence of data for multiple organ failure. In addition, only 61% of all HEP-COVID patients (ICU group unknown) were on prophylactic-intensity anticoagulation<br>q. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes small benefit and large harm; rated down 3 levels for very serious imprecision<br>r. The decision thresholds for Intracranial Hemorrhage were: 18 per 1,000 for Trivial/Small; 35 per 1,000 for Small/Moderate; 68 per 1,000 for Moderate/Large<br>s. In the control group, only 61% of all HEP-COVID patients (ICU group unknown) were on prophylactic-intensity anticoagulation. As higher intensities according to local practice were allowed, not rated down for risk of bias but rated down one level for indirectness<br>t. Unknown effect as no events were observed in the RCT; rated down 2 levels for very serious imprecision<br>u. The decision thresholds for Invasive Mechanical Ventilation (long-term) were: 20 per 1,000 for Trivial/Small; 38 per 1,000 for Small/Moderate; 74 per 1,000 for Moderate/Large<br>v. The baseline risk comes from one RCT, not observational studies, and may not represent risk in practice. In addition, only 61% of all HEP-COVID patients (ICU group unknown) in the control group were on prophylactic-intensity anticoagulation<br>w. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes large harm and large benefit; rated down 3 levels for very serious imprecision<br>x. The decision thresholds for Limb Amputation were: 21 per 1,000 for Trivial/Small; 41 per 1,000 for Small/Moderate; 80 per 1,000 for Moderate/Large<br>y. The reported outcome was 'major adverse limb event'. In addition, only 61% of all HEP-COVID patients (ICU group unknown) in the control group were on prophylactic-intensity anticoagulation<br>z. The 95% CI of the absolute effect estimate crosses multiple decision thresholds and includes large harm and large benefit; rated down 3 levels for very serious imprecision<br>aa. Data from one RCT, small sample size of 83; rated down 3 levels for very serious imprecision | |

## Certainty of evidence

What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | Multiple critical outcomes were rated as very low certainty evidence. | There was consensus among the panel that the overall certainty of evidence for desirable and undesirable effects was very low. Depending on the outcome, this was primarily due to very serious imprecision, serious risk of bias and/or serious indirectness. |

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | The relative importance of the outcomes reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting less impairment and lower values reflecting greater impact on life. A systematic review of observational studies (10) suggests that affected people place a moderate relative value on avoiding pulmonary embolism, DVT, major bleeding and a low relative value (indicating great impairment on outcomes such as intracranial bleeds). There is moderate to high certainty in these findings. The evidence suggests that there is variability around these values or relative importance that the affected population places on these outcomes, but this may be a result of the way they are measured. Below is the research evidence as synthesized. Survey results with ASH VTE guideline panels using visual analogue scales showed lower values than the one described below, and this is explained by the fact that methods such as the standard gamble produce results that suggest less impairment of health.<br><br>**<u>The relative importance of the outcomes* was as follows in the identified studies:</u> Pulmonary embolism: 0.63-0.93** (3), (11), (1) - survey of ASH panelists: 0.25 for severe to 0.62 for mild)**Deep vein thrombosis: 0.64-0.99** (3), (11), (12), (13) - survey of ASH panelists: 0.43 for severe to 0.71 for mild)**Deep vein thrombosis patients' own current health: 0.95 (Time trade off)** (1)**Major bleeding as indicated by gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)** (3), (1) - survey of ASH panelists: 0.44)**Muscular bleeding: 0.76 (time trade off)** (1)**Minor intracranial bleeding event: 0.75 (standard gamble)** (3)**Major intracranial bleeding event: 0.15 (standard gamble)** (3)**Central nervous system bleeding: 0.29-0.60 (standard gamble)** (6), (4)**Treatment with LMWH: 0.993 (time trade off)** (9)* indicated by utility value where 0 = death and 1.0 = full health<br><br>**<u>Studies described the following regarding the relative importance of outcomes and patients' preferences for VTE prophylaxis:</u>** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis (2), (1), (5), (7) and that they would like to avoid adverse events but most of them are "not afraid of" the adverse events (14), (2), (4), (5), (7). Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; patients would like to avoid adverse events but most of them are "not afraid of" the adverse events.<br><br>**<u>Studies additionally described the following regarding the relative importance of outcomes and patients' preferences for the pharmacological prophylaxis:</u>**Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (8). | 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.<br><br>Panel members also note that there is probably no important uncertainty or variability for outcomes such as multi-organ failure, invasive mechanical ventilation, and limb amputation. |

## 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<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | | Although the panel judged the overall certainty of evidence to be very low, they also judged that the moderate harms likely outweigh the small benefits of therapeutic-intensity anticoagulation. |

## Resources required

How large are the resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>● Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | **Cost of interventions (selected)**<br><br>**Monthly drug prices (US) are listed.**<br><br><br>**<u>Prophylactic-intensity anticoagulation</u>**<br><br>**Apixaban 2.5 mg po BID $520.71**<br><br>**Betrixaban 80 mg $472.65**<br><br>**Dabigatran 75 mg $240.41**<br><br>**Dalteparin 5,000 U $1,326.91**<br><br>**Enoxaparin 40 mg $176.75**<br><br>**Fondaparinux 2.5 mg/0.5 ml $313.20**<br><br>**Heparin SQ 5,000 U BID $34.91**<br><br>**Rivaroxaban 10 mg $508.72**<br><br><br>**<u>Therapeutic-intensity anticoagulation</u>**<br><br>**Apixaban 5 mg po BID $533.01**<br><br>**Dabigatran 75, 110 or 150 mg BID $458.65**<br><br>**Dalteparin 15,000 U $3,767.54** | This comparison focused on differences in drug costs between prophylactic-intensity versus therapeutic-intensity anticoagulation.<br><br>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.<br><br>It was noted that the costs of certain anticoagulants may vary geographically. |

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|---|---|---|
| | **Enoxaparin 80 mg BID $326.73**<br><br>**Fondaparinux 7.5mg/0.6 ml $466.73**<br><br>**Fondaparinux 10mg/0.8 ml $857.39**<br><br>**Heparin SQ 20,000 U BID $190.00**<br><br>**Rivaroxaban 20 mg $520.72**<br><br>**Warfarin INR 2.0 - 3.0 $4.96 (only drug cost - monitoring not included)**<br><br>https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html (Feb 17, 2022)<br><br>http://www.goodrx.com/ and https://www.drugs.com/price-guide/ (Feb 17, 2022) | |

## Certainty of evidence of required resources

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

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● 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<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | No research evidence identified. | Given the uncertainty about the baseline risks and effects of therapeutic-intensity anticoagulation in critically ill 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<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ 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. In addition, the panel highlighted the racial disparity between RCT enrolment and the COVID-19 population at large. 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<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Acceptability and use of higher versus lower doses of pharmacological prophylaxis:<br><br>**With regards to different anticoagulants, we previously identified the following research that related to acceptability.**<br><br>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. (15)<br><br>Among 250 hospitalized (surgical and medical) patients, initiation of prescribed therapy was 95% for LMWH, 88% for UFH 3/day and 87% for UFH 2/day. All scheduled doses were received by 77% on LMWH, 54% on UFH 3/day and 45% on UFH 2/day. Patient refusal explained 39% of omitted LMWH and 44% of omitted UFH doses. LMWH was less likely to be administered in surgical than in medical patients. (16)<br><br>A survey among 1,553 Canadian health care providers showed that DVT prophylaxis was perceived as important by all provider groups, but this did not appear to translate into knowledge about underutilization of current DVT prophylaxis strategies. Physicians and pharmacists recognized the underuse of DVT prophylaxis in medical patients, while nurses and physiotherapists tended to perceive prophylaxis strategies as appropriate. Lack of clear indications and contraindications for prophylaxis and concerns about bleeding risks were perceived as important barriers. Preprinted orders were considered the most potentially successful and feasible way to optimize prophylaxis. (17)<br><br>One large study using databases in the US found that the majority of at-risk hospitalized medically ill patients do not receive VTE prophylaxis. Only 18% of at-risk patients received VTE prophylaxis on day 1 or 2 in hospital, typically with LMWH (56% of patients receiving prophylaxis), pneumatic compression device (25%), vitamin K antagonist use (16%), or graduated compression stockings (11%). Use of prophylaxis exceeded 25% only in patients admitted from nursing homes and those with prior VTE. (18) | The acceptability of the intervention to various stakeholders (patients, healthcare providers, institutions, etc.) was considered.<br><br>The intervention was felt to be acceptable to patients.<br><br>The intervention was felt to be acceptable to providers. However, the panel acknowledged that given the very low certainty in evidence, there may be regional variation in acceptability of the intervention. |

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|---|---|---|
| | Prescribing and uptake in different settings: Among 170 medical patients eligible for VTE prophylaxis, 54% received pharmacological VTE prophylaxis and 25% received non-pharmacological VTE prophylaxis due to a contraindication for pharmacological prophylaxis. (19)<br><br>Among 64 medical patients, 59% received appropriate VTE prophylaxis using LMWH. (20) | |

## Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | Feasibility of using higher versus lower doses of anticoagulants.<br><br>**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. (21)A survey among ICU directors, bedside pharmacists, thromboprophylaxis research coordinators and physician site investigators in 27 Canadian ICU's, showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. Top five reported facilitators were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. Acceptability of facilitators varied across ICU's. (22) | The intervention was felt to be feasible as therapeutic-intensity anticoagulation is already used broadly in the management of critically ill patients with or without COVID-19. |

# SUMMARY OF JUDGEMENTS

| CRITERIA | JUDGEMENTS | IMPORTANCE FOR DECISION |
|---|---|---|
| PROBLEM | Yes | |
| DESIRABLE EFFECTS | Small | |
| UNDESIRABLE EFFECTS | Moderate | |
| CERTAINTY OF EVIDENCE | Very low | |
| VALUES | Possibly important uncertainty or variability | |
| BALANCE OF EFFECTS | Probably favors the comparison | |
| RESOURCES REQUIRED | Negligible costs and savings | |

| CRITERIA | JUDGEMENTS | IMPORTANCE FOR DECISION |
|---|---|---|
| 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 American Society of Hematology (ASH) guideline panel suggests using prophylactic-intensity over therapeutic-intensity anticoagulation for patients with COVID-19-related critical illness who do not have suspected or confirmed venous thromboembolism (VTE) (conditional recommendation based on very low certainty in the evidence about effects).

**Remarks:**

- 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.
- A separate recommendation (1A) addresses the comparison of intermediate-intensity and prophylactic-intensity anticoagulation in critically ill COVID-19 patients.
- 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 have been validated in hospitalized COVID-19 patients (critically or non-critically ill), 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 low bleeding risk and high thrombotic risk.
- At present, there is no direct high-certainty evidence comparing different types of anticoagulants in patients with COVID-19. Unfractionated or low molecular weight heparin were used in most of the identified studies.
- This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation or continuous renal replacement therapy.

## Justification

**Overall justification**

Although the panel judged the overall certainty of evidence to be very low for both desirable and undesirable effects, the panel judged that the moderate harms would outweigh the small benefits of therapeutic-intensity anticoagulation. The panel therefore suggested prophylactic-intensity rather than therapeutic-intensity anticoagulation in patients with COVID-19-related critical illness while acknowledging that individualized decision-making is required. This recommendation will continue to be updated based on a living review of evolving evidence.

**Detailed justification**

*Balance of effects*

While there was a suggestion of a small reduction in pulmonary embolism with therapeutic-intensity anticoagulation, this evidence was of very low certainty. Trivial-to-moderate harms were observed for multiple critical outcomes including mortality, major bleeding, invasive mechanical ventilation, multiple organ failure, and limb amputation, at least some of which were felt to be independent. Taken together, the panel judged the aggregate harm of the intervention to be moderate, albeit based on very low certainty in the evidence. The panel acknowledged that an individualized decision is important for each patient based on an assessment of thrombotic and bleeding risk. The panel emphasized that there is a need for more high-quality randomized controlled trials examining this question.

## 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 to estimate thrombotic risk in hospitalized patients (critically or non-critically ill) have been validated in COVID-19 patients, with modest prognostic performance. No risk assessment models for bleeding have been validated in COVID-19 patients. The panel acknowledges that lower-intensity anticoagulation may be preferred for patients judged to be at low thrombotic risk and high bleeding risk.

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## Monitoring and evaluation

Patients receiving anticoagulant therapy require regular reassessment of thrombotic and bleeding risk. It is important to frequently assess and optimize factors that affect the safety of anticoagulation (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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1. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv* 2018; 2(22): 3257-3291.

## Research priorities

- Additional large, high-quality randomized controlled trials to increase the certainty of the evidence on health effects
- Studies assessing baseline VTE risk, major bleeding risk, and mortality in critically ill patients on prophylactic-intensity anticoagulation therapy
- Studies examining the impact of non-anticoagulant interventions (e.g., vaccines, corticosteroids, antiviral therapies, antiplatelet therapies, anticytokine therapies, monoclonal antibody therapies) on thrombotic risk
- Studies examining the impact of different viral variants on thrombotic risk
- Development and validation of risk assessment models for thrombosis and bleeding in patients with COVID-19 related critical illness
- Studies examining the impact of anticoagulant therapy on thrombosis and bleeding outcomes in patients of differing race/ethnicity
- Studies estimating the relative disutility of thrombotic and bleeding outcomes in patients with COVID-19 related critical illness

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