Anticoagulation

A Review of Pertinent Drug Information for SARS-CoV-2

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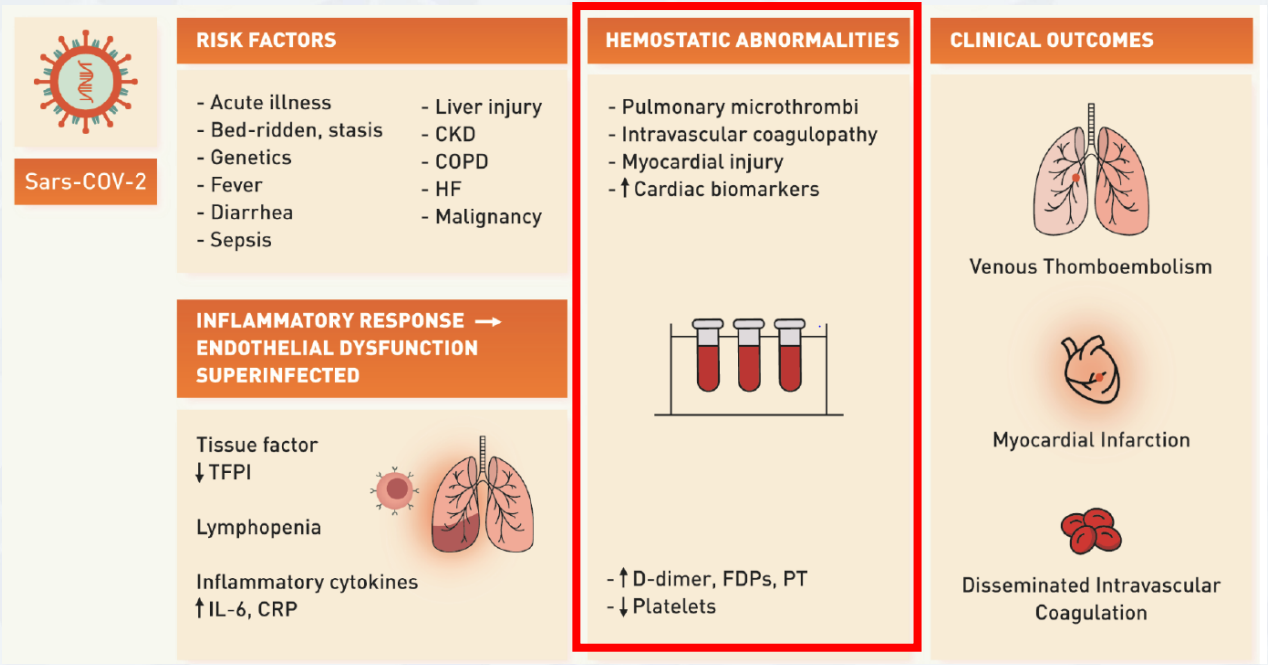
Data as of 4.21.2021

Mechanisms of thrombotic risk



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Bikdeli B, et al. J Am Coll Cardiol. 2020 Apr 15. doi: 10.1016/j.jacc.2020.04.031.

COVID-19 and Hemostasis Parameters

- Disease severity associated with:
  - ↑ prothrombin time (PT)
  - ↑ international normalized ratio (INR)
  - ↑ thrombin time (TT)
  - ↓ activated partial thromboplastin time (aPTT)

Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19.

Zhang Y[1], Xiao M[1], Zhang S[1], Xia P[1], Cao W[1], Jiang W[1], Chen H[1], Ding X[1], Zhao H[1], Zhang H[1], Wang C[1], Zhao J[1], Sun X[1], Tian R[1], Wu W[1], Wu D[1], Ma J[1], Chen Y[1], Zhang D[1], Xie J[1], Yan X[1], Zhou X[1], Liu Z[1], Wang J[1], Du B[1], Qin Y[1], Gao P[1], Qin X[1], Xu Y[1], Zhang W[1], Li T[1], Zhang F[1], Zhao Y[1], Li Y[1], Zhang S[1].

Antiphospholipid antibodies	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG

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Yang X, et al. Lancet Respir Med. [Epub ahead of print]. doi: 10.1016/S2213-2600(20)30079-5.
Zhang Y, et al. N Engl J Med. 2020;18(4):844-847. doi: 10.1111/jth.14768.

Consequences of hemostasis parameter abnormalities

Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

Ning Tang, Dengju Li, Xiong Wang, Ziyong Sun

First published:19 February 2020 | https://doi-org.proxy.lib.umich.edu/10.1111/jth.14768 |

Future research should focus on optimal anticoagulant monitoring parameters for COVID-19 patients on unfractionated heparin.

If aPTT is low in these patients, adjustments to heparin dosing to reach therapeutic levels may result in over-anticoagulation.

Unknown impact on anti-Xa levels though current recommendations suggest using anti-Xa instead of aPTT for monitoring heparin.

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Tang N, et al. J Thromb Haemost. 2020;18(4):844-847. doi: 10.1111/jth.14768.
Barnes G, et al. J Thromb Thrombolysis. 2020;50(1):72-81.

Incidence of thrombotic events

21%
✓ VTE prophylaxis

25%
✖VTE prophylaxis

31%
✓ VTE prophylaxis*

Abbreviations: VTE=venous thromboembolism
*VTE prophylaxis was underdosed in 2 of the 3 centers

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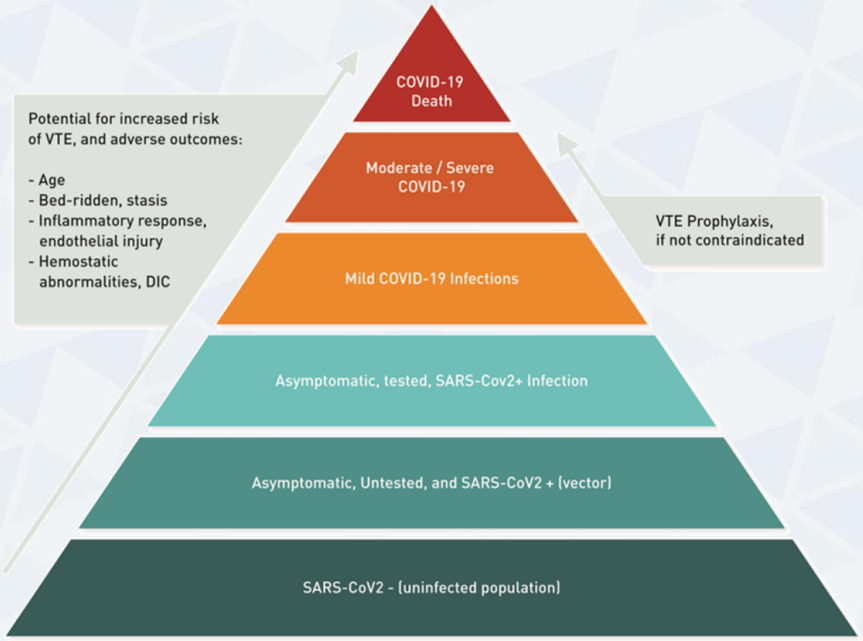
Lodigiani C, et al. Thromb Res. 2020 Apr 23. doi:10.1016/j.thromres.2020.04.024.
Cui S, et al. J Thromb Haemost. 2020 Apr 9. doi:10.1111/jth.14830.
Klok FA, et al. Thromb Res. 2020 Apr 10. doi: 10.1016/j.thromres.2020.04.013.

Prevention of thromboses



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What prophylactic doses should be used?

Local protocol for thromboprophylaxis in participating centres for patients admitted to the intensive care unit during the study period.

Site	
Leiden University Medical Center	nadroparin 2850 IU sc per day or 5700 IU per day if body weight > 100 kg
Erasmus University Medical Center	Nadroparin 5700 IU per day; nadroparin 5700 IU sc twice daily from April 4th 2020 and onwards
Amphia Hospital Breda	Nadroparin 2850 IU sc per day or 5700 IU per day if body weight > 100 kg; nadroparin 5700 IU sc per day from March 30th 2020 and onwards

Author Conclusions:

Pharmacological prophylaxis in all COVID-19 patients admitted to the ICU, and suggest increasing prophylactic doses towards high-prophylactic doses even in the absence of randomized evidence.

Current Recommendations:

For critically ill patients with confirmed or highly suspected COVID-19, **we suggested increased doses of VTE prophylaxis** (ex. enoxaparin 40mg SQ BID, enoxaparin 0.5mg/kg SQ BID, heparin 7500units TID, or low-intensity heparin infusion)

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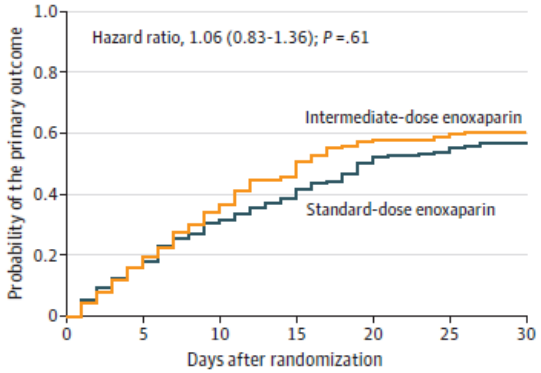
Klok FA, et al. Thromb Res. 2020 Apr 10. doi: 10.1016/j.thromres.2020.04.013.
Barnes G, et al. J Thromb Thrombolysis. 2020;50(1):72-81.

Effect of intermediate-dose vs standard-dose prophylactic anticoagulation – INSPIRATION trial results



No. of patients at risk

Intermediate dose							
Total	276	235	196	175	156	154	150
Primary outcome	0	41	39	21	19	2	4
All-cause mortality	0	37	41[a]	20	16	2	2
VTE	0	4	1	1	2	0	0
Ischemic stroke	0	0	0	0	1	0	0
Standard dose							
Total	286	244	211	194	173	167	160
Primary outcome	0	42	33	17	21	6	7
All-cause mortality	0	38	29	17[a]	21[a]	6	6
VTE	0	3	4	1	2[b]	0	1
Ischemic stroke	0	1	0	0	0	0	0

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Sadeghipour P, et al. JAMA. 2021;e214152. doi: 10.1001/jama.2021.4152.

Role of direct oral anticoagulants for VTE prophylaxis

- Studies for extended VTE prophylaxis in medically ill patients:
  - APEX: oral betrixaban 80mg daily for 35-42 days
  - MARINER: oral rivaroxaban 10mg daily for 45 days

☒ Incidence of symptomatic VTE

VTE Risk Factor	VTE Risk Score
Previous VTE	3
Known thrombophilia	2
Current lower limb paralysis or paresis	2
History of cancer	2
ICU/CICU stay	1
Complete immobilization ≥1 day	1
Age ≥ 60 years	1

Risk stratification from MARINER:

- IMPROVE score ≥4
- IMPROVE score 2-3 and D-dimer more than 2x ULN

Abbreviations: VTE=venous thromboembolism; ICU=intensive care unit; CICU=cardiac intensive care unit; ULN=upper limit of normal

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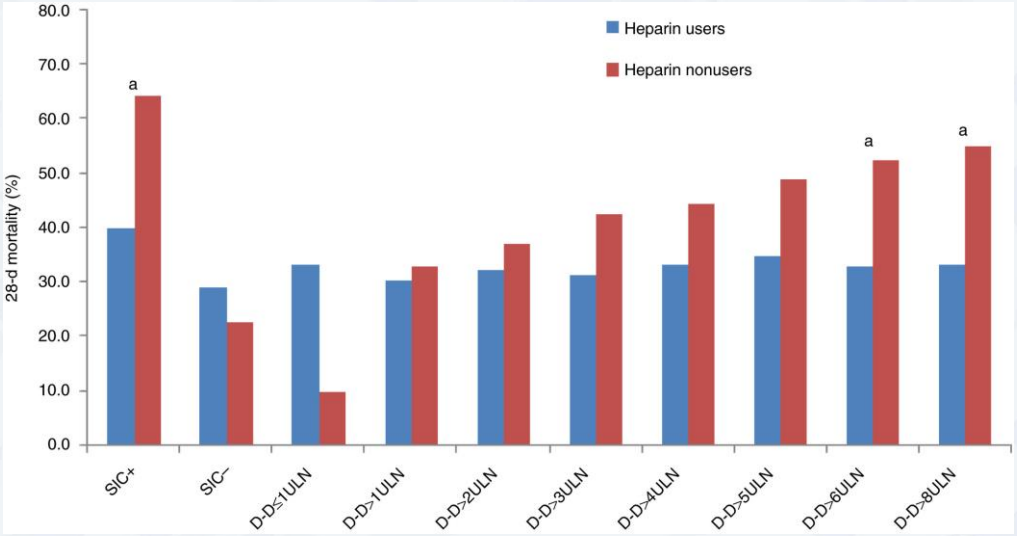
Cohen AT, et al. N Engl J Med 2016; 375:534-544. doi: 10.1056/NEJMoa1601747.
Spyropoulos AC, et al. N Engl J Med 2018; 379:1118-1127. doi: 10.1056/NEJMoa1805090.

Role for empiric anticoagulation



Abbreviations: D-D=D-dimer; SIC +=SIC score≥4; SIC-=SIC score <4; ULN= upper limit of normal; a=P<0.05 between heparin users and nonusers

LMWH was the most commonly used anticoagulant in our hospital for preventing DIC and VTE in patients, also because of its anti-inflammatory effect.[16] Another reason is that other anticoagulants, such as recombinant soluble thrombomodulin or antithrombin, is unavailable in China. The prophylactic dose of LMWH was used in most of our heparin users, bleeding complications were unusual and commonly mild, and it is not known if higher doses would have been better. Because the evidence suggests that the prevalence and genetic risk factors of VTE vary significantly among ethnic populations, and the incidence of VTE in Asian populations (21-29 cases per 100 000 individuals per year) is low,[17,18] a higher dose of LMWH could be considered in non-Asian patients with severe COVID-19.

Doses used in the study:
Enoxaparin: 40-60mg daily
Unfractionated heparin: 10,000 to 15,000 units daily

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Tang, et al. J Thromb Haemost. 2020 Mar 27. doi:10.1111/jth.14817.

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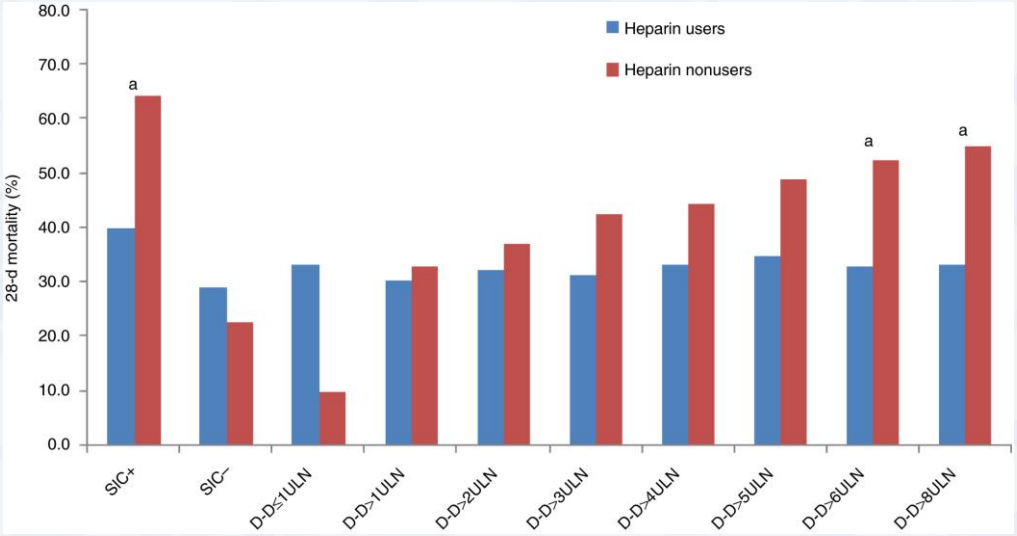

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Emerging evidence

NEWS RELEASES

Tuesday, December 22, 2020

NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patients

- Design: randomized, open-label, adaptive Bayesian trial
- Patients: adults hospitalized patients for COVID-19
  - Randomized within 72 hours of admission
  - 48 hours in REMAP-CAP for ICU patients
- Intervention:
  - Therapeutic low molecular weight heparin or unfractionated heparin
  - Therapeutic dose as per hospital policy for treatment of VTE
- Control:
  - Usual care pharmacologic VTE prophylaxis
- Duration:
  - 14 days or hospital discharge (or liberation from supplemental oxygen; ATTACC)

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Cuker, et al. Blood Adv. 2021. 5(3):872-888. doi:10.1182/bloodadvances.2020003763.

Interim analysis results

State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	**Superiority** [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	**Superiority** [Probability of OR>1 = 0.991]
Moderate state, missing D-dimer	1.51 (1.06 – 2.15)	n/a⏃
Severe state	0.76 (0.60 – 0.97)	**Futility*** [Probability of OR>1.2 < 0.001]

* Posterior probability of **inferiority** [Probability of OR<1 = 0.985]
⏃ Not evaluated for stopping at interim

Interim conclusions

- **Moderate state:**
  - Therapeutic dose superior to usual care VTE prophylaxis with regard to organ support-free days in each d-dimer subgroup
  - Positive effect across morbidity and mortality components of primary endpoint
  - Major bleeding rate <2% on therapeutic anticoagulation
- **Severe state:**
  - Therapeutic heparin does not improve outcomes at day 21
  - Therapeutic heparin may be harmful compared to thromboprphyalxis
  - Numeric increase in major bleeding

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Guideline recommendations

Questions	NIH recommendations	ASH recommendations
Should acutely ill hospitalized patients with confirmed or highly suspected COVID-19 receive VTE prophylaxis?	Hospitalized nonpregnant adults with COVID-19 should receive **prophylactic dose anticoagulation**. Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19.	Suggests using **prophylactic-intensity** over intermediate-intensity or 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).
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COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/.

Considerations for VTE medical treatment

- **Unfractionated heparin (UFH)**
  - Short half-life if procedures are planned
  - Increased healthcare worker exposure
  - Time to achieve therapeutic levels
- **Low molecular weight heparin (LMWH)**
  - Renal dysfunction
  - Dosing with obesity
  - Levels for prolonged therapy
- **Direct oral anticoagulants (DOACs)**
  - Renal dysfunction
  - Drug-drug interactions

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Potential drug interactions between anticoagulants and investigational therapies

Investigational COIVD-19 Therapies	Vitamin K antagonists	Dabigatran	Edoxaban
Lopinavir/ritonavir	**CYP2C9 induction:** May decrease plasma concentration. Dose increases may be necessary.	**P-gp inhibition:** May increase plasma concentration. No dose adjustment recommended.	**P-gp inhibition:** Do not co-administer
Tocilizumab	-	-	-
Ribavirin	**Unknown mechanism:** Possible decreased absorption of warfarin. Increased dose may be needed.	-	-
Methylprednisolone	**Unknown mechanism:** Decreased dose may be needed	-	-
Sarilumab	-	-	-
Azithromycin	**Unknown mechanism:** Decreased dose may be needed	**P-gp inhibition:** May increase plasma concentration. No dose adjustment recommended.	**P-gp inhibition:** Limit dose to 30mg daily for VTE treatment
Hydroxychloroquine and Chloroquine	-	-	-

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Potential drug interactions between anticoagulants and investigational therapies

Investigational COIVD-19 Therapies	Apixaban	Rivaroxaban
Lopinavir/ritonavir	**CYP3A4 and P-gp inhibition:** Administer 50% of dose (do not administer if initial dose is 2.5mg BID)	**CYP3A4 and P-gp inhibition:** Do not co-administer
Tocilizumab	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended
Ribavirin	-	-
Methylprednisolone	-	-
Sarilumab	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended
Azithromycin	-	-
Hydroxychloroquine and Chloroquine	-	-

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Summary

- Hospitalized patients with COVID-19 are at high thrombotic risk
- VTE prophylaxis should be utilized in all acutely ill patients with no contraindications including those in the ICU
- Unclear role of empiric therapeutic anticoagulation
- Consider utilizing DOACs in eligible patients for treatment of VTE to minimize monitoring

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Future directions

Study title	Interventions	Estimated study completion
Coagulopathy of COVID-19: a pragmatic randomized controlled trial of therapeutic anticoagulation vs standard care	Therapeutic anticoagulation with LMWH or UFH vs thromboprophylaxis	December 2020
Intermediate or prophylactic-dose anticoagulation for venous or arterial thromboembolism in severe COVID-19	LMWH prophylaxis dose LMWH intermediate dose UFH infusion UFH SQ	April 2021
Preventing COVID-19 complications with low-and high-dose anticoagulation	Therapeutic anticoagulation with LMWH or UFH vs thromboprophylaxis (higher dose in ICU)	November 2020
Nebulised rt-PA for ARDS due to COVID-19	rt-PA vs standard of care for ARDs	January 2021
Thrombosis and COVID-19	Thromboelastometry in patients hospitalized for COVID vs hospitalized with thrombosis	December 2020

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