ANTIKOAGULACIJA I COVID-19
najčešće postavljana pitanja

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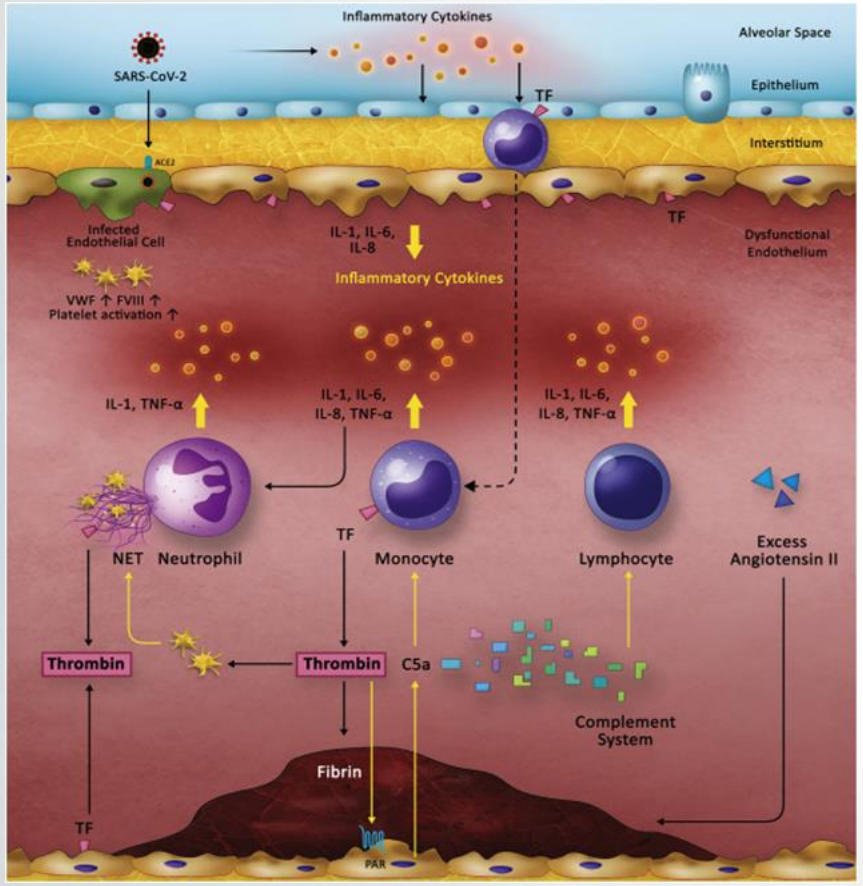
Uvod

- Koagulopatija u sklopu COVID 19 (arterijski i venski tromboembolizam) predstavlja najozbiljniju posljedicu oboljenja i prognostički je loš znak.
- Za sada ne postoji jasan patofiziološki mehanizam nastanka hiperkoagulabilnosti.
- Jedna od hipoteza govori u prilog pojačanog imunološkog odgovora koji dovodi do trombo-inflamacije kroz više mehanizama: aktivacija komplementa, citokinska oluja i endotelitis.
- Druga hipoteza govori u prilog da sam virus dovodi do aktivacije zgrušavanja.

Patofiziološki mehanizam- šta do sada znamo

- Virhowova trijada: staza, hiperkoagulabilnost, endotelna ozljeda
- Karakteristično je povećanje D dimera i fibrinogena, praćeno umjerenim produženje protrombinskog vremena i aktiviranim parcijalnim tromboplastinskim vremenom (aPTT), uz umjereni pad ili porast trombocita.
- Razlika u odnosu na DIC: COVID 19- tromboza vs DIC- krvarenje (hronično)

Patofiziološki mehanizam - šta pretpostavljamo



- SARS CoV2 virus ulazi u stanicu preko ACE2 receptora, što dovodi do pojačanog inflamatornog odgovora u alveoli
- Aktivacija epitelnih stanica, MF i monocita
- Endotelna disfunkcija, povišena ekspresija TF, aktivacija PLT i povećanje koncentracije VWF i FVIII što dovodi do pojačanog stvaranja trombina te ugruška
- Trombin djeluje na trombocite, koji stvaraju mrežu za neutrofile koji dalje dovode do aktivacije monocita preko C5a

*M.Y. Abou-Ismail, et al. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thrombosis research. VOLE 194, P101-115, Oct 01, 2020

Koja vrsta trombotskog događaja je češća?

Venski tromboembolizam

- Najčešća manifestacija je plućna embolija
- Češća među kritično oboljelim pacijentima
- Čak i pacijenti koji su bili na profilaktičkoj dozi LMWH su razvili VTE u 27%, od čega je najviše razvilo PE, čak 81% [1]
- Pacijenti sa ARDS u sklopu COVID 19 su razvili gotovo 6x češće PE u odnosu na pacijente sa ARDS drugog porijekla (11.7% vs 2.1%, OR 6.2, p = 0.008) [2]

1. Klok F.A. et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb. Res. 2020; 191: 145-147
2. Helms J. 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

Arterijska tromboza

- Znatno rijeđa od venske
- Infarkt miokarda i ACS zabilježeni kod 1.1% pacijenata sa COVID 19 [1]
- Ishemijski moždani udar znatno češći kod pacijenata mlađe životne dobi [2]
- Mikrovaskulrne tromboze: pronađene čak i u organima koji nisu zahvaćeni covidom- koža, bubrezi, crijeva [3]

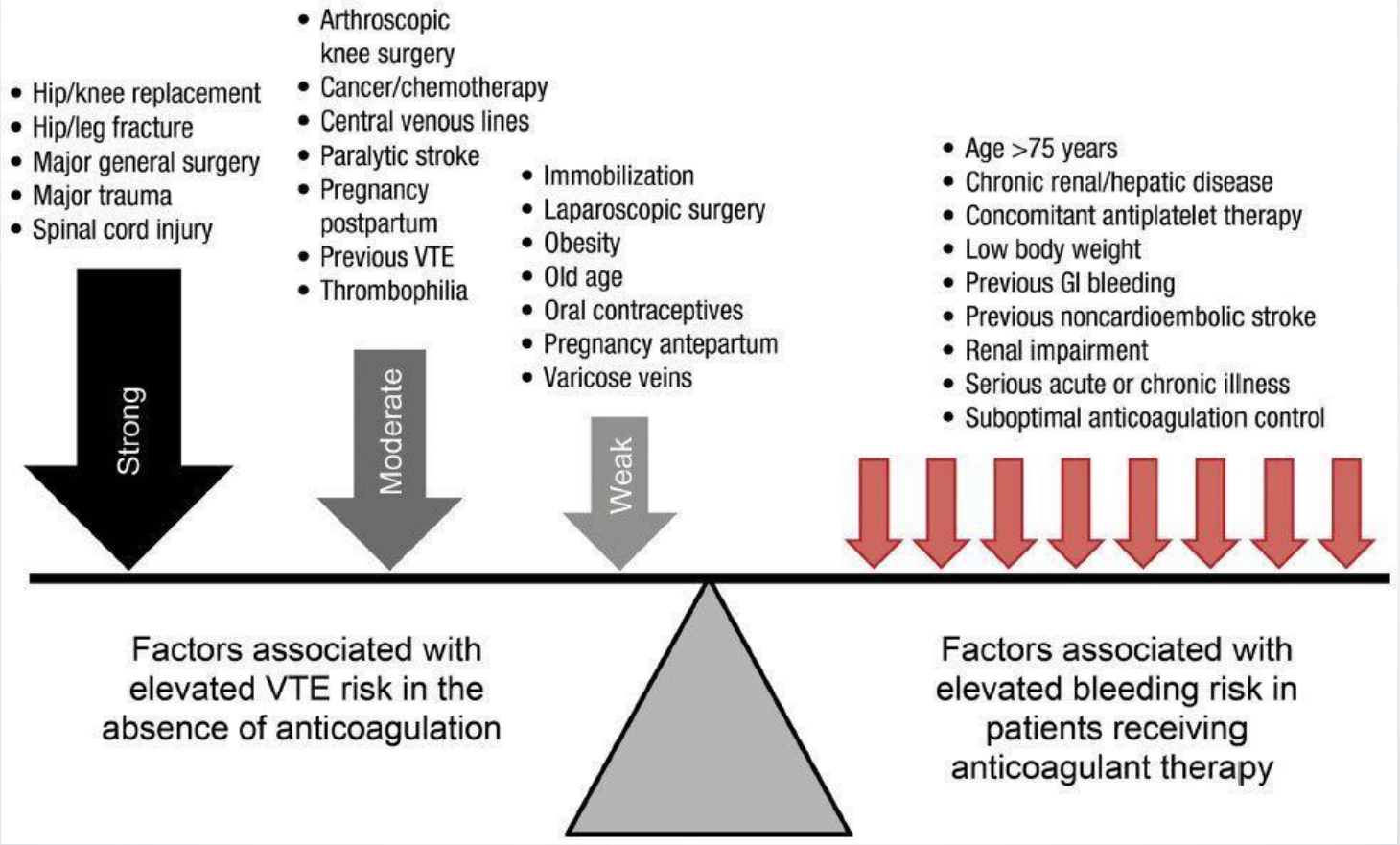
1. Lodigiani C. et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan. Italy. Thromb Res. 2020; 191: 9-14

2. Oxley T.J. et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N. Engl. J. Med. 2020; 382: e60

3. Magro C.et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl. Res. 2020; 220: 1-13

Kako procijenti rizik da li će nastupiti tromboza ili krvarenje?

Krvarenje vs tromboza



Kalkulatori procjene krvarenja:

Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points
H	Hypertension (ie, uncontrolled blood pressure)	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding tendency or predisposition	1
L	Labile INRs (for patients taking warfarin)	1
E	Elderly (age greater than 65 years)	1
D	Drugs (concomitant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2
		Maximum 9 points

HAS-BLED score (total points)	Bleeds per 100 patient-years¶
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5 to 9	Insufficient data

The HAS-BLED bleeding risk score has only been validated in patients with atrial fibrillation receiving warfarin. Refer to UpToDate topics on anticoagulation in patients with atrial fibrillation and on specific anticoagulants for further information and other bleeding risk scores and their performance relative to clinical judgment.

INR: international normalized ratio; NSAIDs: nonsteroidal antiinflammatory drugs.
* Hypertension is defined as systolic blood pressure >160 mmHg. Abnormal renal function is defined as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 micromol/L. Abnormal liver function is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin more than 2 times the upper limit of normal, plus 1 or more of aspartate transaminase, alanine transaminase, and/or alkaline phosphatase more than 3 times the upper limit of normal). Bleeding predisposition includes chronic bleeding disorder or previous bleeding requiring hospitalization or transfusion. Labile INRs for a patient on warfarin include unstable INRs, excessively high INRs, or <60% time in therapeutic range.
¶ Based on initial validation cohort from Pisters R. A novel-user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138:1093. Actual rates of bleeding in contemporary cohorts may vary from these estimates.

Original figure modified for this publication. Lip GY. Implications of the CHA2DS2-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation. Am J Med 2011; 124:111. Table used with the permission of Elsevier Inc. All rights reserved.

VTE-BLEED score

	Points in score
Active cancer	2
Male patient with uncontrolled hypertension	1
Anemia	1.5
History of bleeding	1.5
Kidney dysfunction (CrCl 30 to 60 mL/min)	1.5
Age ≥60 years	1.5

This score was developed from an evaluation of over 2500 individuals with venous thromboembolism in the RE-COVER trials who were assigned to receive dabigatran and verified in over 2500 individuals from the same trials assigned to warfarin. A score of 2 points or higher was associated with a high bleed risk and 0 to 1.5 points with a low bleed risk.

CrCl: creatinine clearance.

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Kalkulatori procjene rizika od tromboze

Wells criteria and modified Wells criteria: Clinical assessment for pulmonary embolism

▪ Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
▪ Other diagnosis less likely than pulmonary embolism	3.0
▪ Heart rate >100	1.5
▪ Immobilization (≥3 days) or surgery in the previous four weeks	1.5
▪ Previous DVT/PE	1.5
▪ Hemoptysis	1.0
▪ Malignancy	1.0
Probability	**Score**
Traditional clinical probability assessment (Wells criteria)	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment (Modified Wells criteria)	
PE likely	>4.0
PE unlikely	≤4.0

DVT: deep vein thrombosis; PE: pulmonary embolism.

Data from van Belle A, Buller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006; 295:172.

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Modified Geneva score

	Variables	Points
Risk factors	Age >65 years	1
	Previous deep venous thrombosis or pulmonary embolism	3
	Surgery under general anesthesia or fracture of the lower limbs within one month	2
	Active malignancy (solid or hematologic; currently active or cured within the last year)	2
Symptoms	Unilateral lower-limb pain	3
	Hemoptysis	2
Signs	Heart rate 75 to 94 beats per minute	3
	≥95 beats per minute	5
	Pain on lower limb deep venous palpation and unilateral edema	4
		Total points
Pre-test probability assessment	Low	0 to 3
	Intermediate	4 to 10
	High	≥11

From Annals of Internal Medicine, Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006; 144(3):165-71. Copyright © 2006 American College of Physicians. All rights reserved. Reprinted with the permission of American College of Physicians, Inc.

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Koga tretirati?
Potvrđen trombotski događaj da,
ali šta je sa ostalim pacijentima?

MENADŽMENT- vanbolnička tromboprofilaksa*

- **Ne započinjati tromboprofilaksu** (antikoagulantnu i antitrombocitnu th) **ukoliko ne postoji druga indikacija!**
- U slučaju postavljene dijagnoze VTE, nastaviti antikoagulantnu terapiju prema preporukama
- U slučaju visokog protrombotskog rizika (ranije VTE, nedavna operacija ili trauma), sve dok pacijent nije u riziku za krvarenje preporučuju se niske doze rivaroxabana 10 mg dnevno 31-35 dana [1]
- MICHELLE studija: tromboprofilaksa po otpustu- rivaroxaban 10 mg vs grupa bez tromboprofilakse: 3%vs 9% (RR, 0.33, 95% CI 0.12-0.9).
- Upotreba ASK nije pokazala signifikantno smanjenje mortaliteta kao i napretka bolesti prema mehaničkoj ventilaciji- Recovery studija[2]

1.Ramacciotti E, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet. 2022;399(10319):50. Epub 2021 Dec 15

2. RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399(10320):143. Epub 2021 Nov 17.

**COVID-19: Hypercoagulability. Available at https://www.uptodate.com/contents/covid-19-hypercoagulability?source=mostViewed_widget#H195437023 (21.02.2022.)

MENADŽMENT-intrahospitalna tromboprofilaksa*

- Svi pacijenti koji su hospitalizirani radi COVID 19 trebaju primati tromboprofilaksu, osim ukoliko ista nije kontraindicirana ili ne zahtjevaju punu terapijsku dozu.
- LMWH ima prednost u odnosu na UFH, osim u slučajevimma teškog bubrežnog oštećenja.
- Preporučuje se doza Enoxaparin 40 mg sc x1 (ukoliko su pacijenti pretili sa tt>120 kg, odnosno BMI>35 kg/m^2- 40 mg x2 sc)
- Terapijska doza je preporučena kod pacijenata sa visokom sumnjom na VTE, a isti se ne može dokazati; ili kod pacijenata sa AF.
- Nastavak antikoagulantne terapije po otpustu ovisi faktorima rizika, komorbiditetima itd

*COVID-19: Hypercoagulability. Available at https://www.uptodate.com/contents/covid-19-hypercoagulability?source=mostViewed_widget#H195437023 (21.02.2022.)

MENADŽMENT- intrahospitalni tretman VTE*

- U slučaju dokazane VTE (ili visoke opravdane sumnje), indicirana je terapijska doza:

1. LMWH 1mg/kg TT x2 sc, ili
2. UFH- doza se titrira u odnosu na vrijednost aPTT ili aktivnosti antifaktor Xa (ukoliko pacijent ima produžen aPTT na samom početku, dozu ordinirati u skladu sa vrijednostima aktivnosti anti faktor Xa).

U slučaju HIT, indicirano je korištenje fondaparinuxa.

Covid 19 sam po sebi NIJE indikacija za terapijsku dozu antikoagulantne terapije.

Formiranje tromba u intravaskularnim uređajima je indikacija za terapijsku dozu antikoagulantne terapije.

Rezistencija na heparin!

**COVID-19: Hypercoagulability. Available at https://www.uptodate.com/contents/covid-19-hypercoagulability?source=mostViewed_widget#H195437023 (21.02.2022.)*

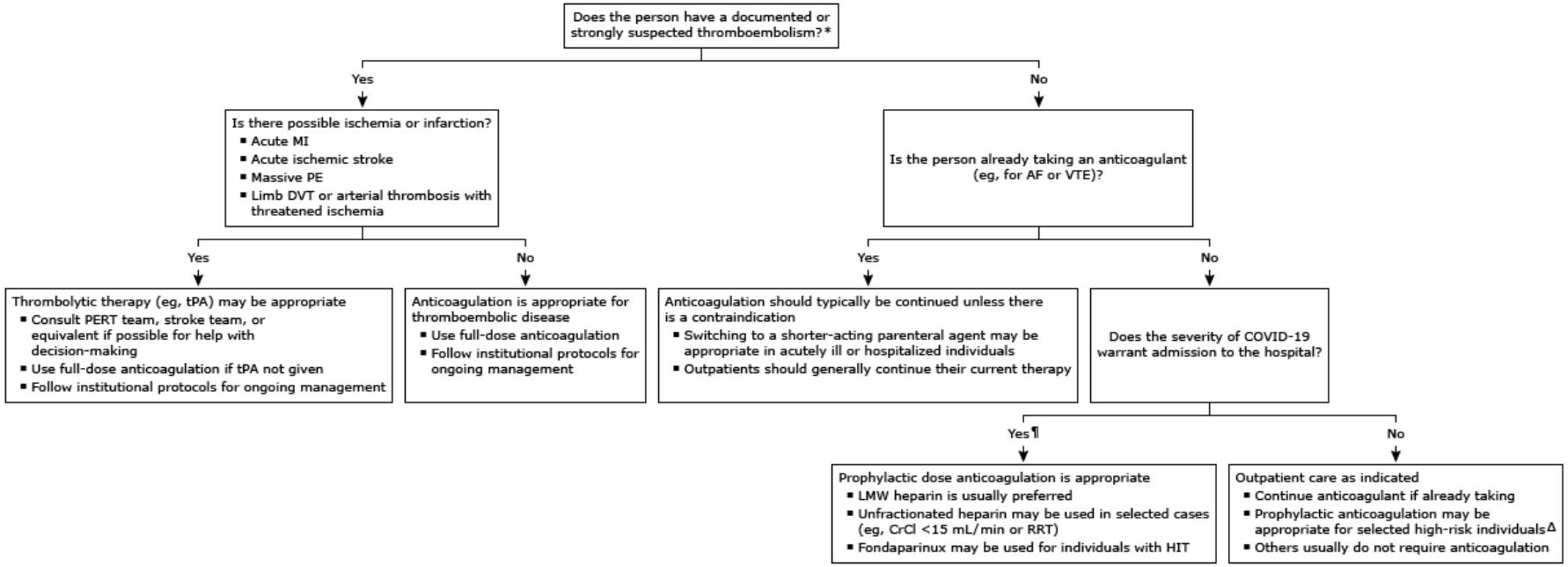
A šta sa trudnicama????

Trudnice i antikoagulancija

- Kod ambulantno tretiranih trudnica radi zaraze SARS CoV2, razmotriti upotrebu antkoagulantne terapije, obzirom da je covid prolazni faktor rizika.
- The Royal College of Obstetricians and Gynaecologists (RCOG) preporučuju profilaktičku upotrebu LMWH kod trudnica zaraženih SARS CoV2, koje su hospitalizirane, bez obzira na formu bolesti.
- Trudnice koje su npr zbog trombofilije na profilaktičkoj dozi LMWH, razmotriti povišenje doze#.

#Jahnavi Daru, Katie White, Beverley J. Hunt,COVID-19, thrombosis and pregnancy,Thrombosis Update, Volume 5, 2021

Anticoagulation in COVID-19 patients



COVID-19 is a hypercoagulable state, and the risk of thromboembolic disease is increased in critically ill (and sometimes well-appearing) individuals. Thromboembolism is typically venous but in some cases may be arterial. Bleeding is much less common but can occur, including intracerebral bleeding, highlighting the importance of documenting ischemia or thrombosis when feasible. Decisions about anticoagulation are made based on clinical criteria as illustrated above, rather than on isolated laboratory findings such as D-dimer, which is primarily used as a measure of disease severity and prognosis.

COVID-19: coronavirus disease 2019; MI: myocardial infarction; PE: pulmonary embolism; DVT: deep vein thrombosis; AF: atrial fibrillation; VTE: venous thromboembolism; tPA: tissue plasminogen activator; PERT: pulmonary embolism response team; ICU: intensive care unit; LMW: low molecular weight; CrCl: creatinine clearance; RRT: renal replacement therapy; HIT: heparin-induced thrombocytopenia.

* Appropriate testing to document suspected thromboembolism is advised if feasible. Assistance from a specialist (pulmonary, critical care, hematology) may be required. Refer to UpToDate for details of testing.

¶ Following publication of randomized trials in March of 2021, VTE prophylaxis using prophylactic-dose anticoagulation (rather than intensified dosing) applies to all individuals hospitalized for COVID-19 who have not had a VTE, regardless of whether they are on a medical ward, surgical ward, obstetric ward (if hospitalized based on COVID-19 severity), or ICU. Adjustment of dosing based on weight may be appropriate, as discussed in UpToDate.

Δ High-risk features include prior VTE, recent surgery or trauma, immobilization, or obesity.

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Hvala na pažnji!