Aleksandar Đenić[1]

NEW ANTICOAGULANT THERAPY ASPECTS TO THE COVID-19 PATIENTS – FROM PROPHYLAXIS TO COMPLICATIONS TREATMENT THERAPY

Summary: COVID-19 patients have a high risk of thrombosis of the arterial and venous systems due to extensive systemic inflammation, platelet activation, endothelial dysfunction, and stasis. D-dimer is an important prognostic marker of mortality caused by COVID-19 patients and its increased values indicate tissue damage and inflammation. The incidence of venous thromboembolism (VTE) is between 16 and 49% as a complication of more severe forms of COVID-19 infection in patients hospitalized in intensive care units. Prophylactic doses of low molecular weight heparin (LMWH) should be given to all hospitalized patients with COVID-19 infection in the absence of active bleeding. The safest way is to adjust the low molecular weight heparin (LMWH) dose according to body weight, especially in obese patients. Unfractionated heparin (UFH) is used in patients with a creatinine clearance of less than 30 ml/min. The therapeutic dose of anticoagulation should be discontinued if the platelet count is $<50 \times 10^9$/L or fibrinogen <1.0 g/L. Clinically significant bleeding events are higher in those who received therapeutic doses compared to those with standard thromboprophylaxis doses. Thrombolytic therapy is recommended in patients with proven pulmonary embolism (PE) and hemodynamic instability or signs of cardiogenic shock, who are not at high risk of bleeding. In hospitalized COVID-19 patients with a high clinical risk of developing venous thromboembolism (VTE) and D-dimer values greater than 2600 ng/ml, the use of therapeutic doses of LMWH in doses adjusted to the patient's body weight should be considered, in the absence of a higher risk of bleeding.

Keywords: COVID-19, D-dimer, venous thromboembolism, pulmonary embolism, low molecular weight heparin, anticoagulant therapy.

[1] Aleksandar Đenić, Special Hospital for Thyroid Diseases and Metabolism Disorders Zlatibor, adjenic74@gmail.com

SARS-COV2 infection complications and thrombosis mechanisms

The SARS-CoV-2 virus causes clinical symptoms of varying severity and affects multiple organs. The clinical picture is especially difficult in elderly patients and patients with comorbidities. Significant complications of COVID-19 infection is coagulopathy, lead to thrombosis and can cause multiorgan damage and lethal outcome (1). COVID-19 coagulopathy is also characterized by microvascular thrombosis. The coagulopathy condition includes increased D-dimer and fibrinogen, increased platelet count, prolonged prothrombin time (PT), leading to a prolonged prothrombotic state that favours venous thromboembolism, especially in severe forms of COVID-19 infection, independent of thromboprophylaxis (2).

Patients with COVID-19 disease have an increased risk of thrombosis of arterial and venous systems due to extensive systemic inflammation, platelet activation, endothelial dysfunction, and stasis. From the present aspect, endothelial dysfunction is considered to be one of the most important mechanisms leading to coagulopathy in COVID-19 disease (3). The SARS-CoV-2 infection leads to a pro-inflammatory state with the activation of several pro-inflammatory cytokines: IL-6, IL-1b, IL-2, IL-4, TNF-alpha, IFN-gamma, C-reactive protein (CRP) and D- dimers. Pro-inflammatory cytokines lead to the activation and replication of pro-inflammatory cells in the circulation leading to endothelial injury, platelet activation and pathological activation of coagulation (4). The SARS-CoV-2 can lead to COVID-19 associated hyper-viscosity and hyperproteinemia, which is an important link between inflammation and coagulopathy. The direct cytotoxic effects of the SARS-CoV-2 virus on endothelial cells are another mechanism that leads to endothelial injury and coagulopathy by binding the "spike" protein of the SARS-CoV-2 virus to ACE2 receptors on the surface of endothelial cells and leading to their damage, activates the coagulation cascade and further production of proinflammatory cytokines (IL-6 and TNF-alpha). IL-6 is a key factor in activating fibrinogen transcription. In patients with more severe forms of COVID-19 disease, hospitalized in intensive care units, high levels of von Willebrand factor (VWF) antigen, increased activity of factor VIII (FVIIIa), soluble P-selectin, have been demonstrated, further confirming endothelial injury during infection. Tang et al., study has been analyzed 183 COVID-19 patients in the intensive care unit. Patients who died from infection were shown to have significantly higher levels of D-dimer and fibrin degradation products (FDP), prolonged prothrombin time (PT), and activated partial thromboplastin time (aPTT) to patients who survived the infection (5). COVID-19 coagulopathy in mild and moderate forms of infection is characterized by elevated fibrinogen, D-dimer and CRP, and minimally prolonged aPTT and PT, as well as a milder form of thrombocytopenia (75–100x10^9/L). In severe forms of COVID-19 infection, coagulopathy is characterized by severe thrombocytopenia (less than 50x10^9/L), decreased fibrinogen levels (less than 1.0 g/L), suggesting

disseminated intravascular coagulation (DIC). In one study of 35 patients who had prolonged aPTT, more than 90% of patients had lupus anticoagulant (LA), the presence of which indicates an associated tendency toward thrombosis and the development of the secondary antiphospholipid syndrome (6).

During COVID-19 infection, complement activation is also involved in coagulation disorders: C3a and membrane-active complex (C5b-9) participate in platelet activation, plasma C5a increase and cellular expression of tissue factor (TF). The interaction between inflammation, complement activation, and the coagulation cascade is crucial in understanding the pathophysiology of COVID-19 disease and is responsible for initiating disseminated intravascular coagulation (7).

In COVID-19 infection, pulmonary intravascular micro thrombosis, as a consequence of alveolar endothelial damage by binding of the SARS-CoV-2 virus to ACE2 receptors of the alveolar epithelium, is thought to lead to the development of hypoxemia in the early stages of acute respiratory distress syndrome (ARDS), cytokine "storm" and hypercoagulability (8). Pulmonary thrombosis (PT) is more common in SARS-CoV-2 infection primarily in the lungs than as a consequence of embolization from deep veins thrombosis (DVT) (9).

Direct viral myocardial and microvascular damage causes subendothelial and collagen exposure, leading to platelet activation, and endothelial trauma leads to tissue factor (TF) pathway activation through FVIIa activation and dysregulation of the kallikrein-kinin system, which contributes to the further coagulation. SARS-CoV-2 and platelet interaction lead to platelet activation and degranulation, which further promotes the prothrombotic vascular condition (10).

D-dimer has a high negative predictive value for pulmonary thromboembolism (PE). In the patient without developing normal D- dimer values are expected to be less than 0.5 μg/mL. D-dimer is an important prognostic marker of mortality in COVID-19 patients and its increased values indicate tissue damage and inflammation (11). D-dimer values > 2 μg/mL (four times higher then upper limit of the reference values) were shown to be a significant predictor of increased in-hospital mortality in one study involving 343 hospitalized patients with COVID-19 disease (sensitivity 92.3%, specificity 83.3 %) (5).

In addition to thrombotic complications in COVID-19 disease, there is an increased risk of bleeding and increased fibrinolytic activity, which is manifested by a significant increase in D-dimer. Proinflammatory cytokines activating endothelial cells lead to the release of plasminogen activator inhibitors-1 (PAI-1) and tPA, which can lead to more significant PAI-1 activity and reduction of thrombolysis (12).

Disseminated intravascular coagulation (DIC) is a potentially lethal mechanism in COVID-19 disease that leads to fibrinolysis disorders and multiorgan dysfunction. Clinical signs of overt DIC include bleeding, thrombocytopenia, prolonged PT, prolonged aPTTT, elevated D dimer, and fibrin degradation products (FDP), and peripheral

micro-angiopathic changes (13). Sepsis-induced coagulopathy (SIC) is a term that defines early DIC, where platelet count and prothrombin time are significantly disrupted in patients with confirmed sepsis. The incidence of DIC in hospitalized COVID-19 patients is 2.2%, and sepsis is included in the pathomechanism in combination with endothelial activation, leukocyte activation, fibrin deposition, which leads to diffuse inflammation and coagulopathy (14).

Thrombocytopenia often occurs in viral infections and SARS-CoV-2 interferes with hematopoiesis in the bone marrow. During micro thrombus formation in the pulmonary circulation, endothelial damage, as well as the hyper-reactivity of platelets, their consumption and decomposition occur, which leads to thrombocytopenia. Thrombocytopenia $<50 \times 10^9$/ L is rarely seen in COVID-19 disease and usually lower values indicate the development of DIC and may use as a prognostic marker of infection severity and increased mortality (15).

Cardiac-specific troponins: Troponinin T (cTnT) and Troponin I (cTnI) are highly sensitive markers of myocardial damage and are elevated in myocardial infarction, myocarditis, and acute pulmonary embolism (PE). Elevated troponin levels in COVID-19 patients can be considered as a marker of poor prognosis and increased mortality (16).

Hospitalized COVID-19 patients have an increased risk of developing venous thromboembolism (VTE). The incidence of venous thromboembolism (VTE) is between 16 and 49% as a complication of more severe forms of COVID-19 infection in patients hospitalized in intensive care units (17). The Dutch study observed the incidence and overall risk of VTE and arterial thrombotic complications in 184 COVID-19 patients, where an incidence of 31% of thrombotic events was found, of which pulmonary embolism (PE) was the most common thrombotic complication (81% of all thrombotic events). In addition to systemic inflammation and endothelial dysfunction, significant risk factors include dehydration, gastrointestinal complications, immobilization, obesity, and other associated comorbidities (diabetes, hypertension, heart failure) (18).

Pharmacological thromboprophylaxis and venous thromboembolism therapy in COVID-19 patients

Current recommendations are that prophylactic doses of low molecular weight heparin (LMWH) should be given to all hospitalized patients with COVID-19 infection in the absence of active bleeding or if they have thrombocytopenia (platelet count less than $25x10^9$) or fibrinogen levels less than 0.5 g / L. According to current guidelines, abnormal PT and aPTT values are not a contraindication for the use of pharmacological thromboprophylaxis, in the absence of active bleeding. If pharmacological prophylaxis is contraindicated, mechanical thromboprophylaxis should be used (19).

Low-molecular-weight heparin (LMWH) is recommended as first-line therapy, and unfractionated heparin (UFH) in patients with creatinine clearance less than 30 ml/min. Both, low molecular weight and unfractionated heparin, have a secondary benefit in COVID-19 patients due to secondary anti-inflammatory and antiviral effects. Heparins bind spike proteins of the SARS-CoV-2 virus and reduce circulating IL-6 levels (20).

It is recommended to measure anti-Xa levels to monitor unfractionated heparin (UFH) and monitor its therapeutic effect, given possible artefact abnormalities of PTT and aPTT during COVID-19 infection and possible heparin resistance. There are no instructions that recommend dosing LMWH relative to anti-Xa levels. The safest way is to adjust the dose of low molecular weight heparin (LMWH) according to body weight, especially in obese patients. The therapeutic dose of anticoagulation should be discontinued if platelet count $<50 \times 10^9$ / L or fibrinogen <1.0 g/L (19).

The clinical benefit of "enhanced" or "high-dose" thromboprophylaxis using high doses (often twice the standard prophylactic dose), although less than therapeutic doses, remains controversial. Several observational studies from the USA, the Netherlands, France and China suggest that routine prophylactic doses of anticoagulants may be insufficient to prevent VTE in high-risk COVID-19 patients, especially in those with elevated coagulation parameters: D dimer, PT, aPTT. This applies to the patients admitted to intensive care units, where the incidence of primarily venous thrombotic complications ranges from 31% to 69% in COVID-19 patients. It remains unclear whether treatment with therapeutic doses of anticoagulant therapy improves outcome, without an increased risk of bleeding in patients who are clinically suspected of having VTE (21).

A large retrospective cohort study of 2773 hospitalized COVID-19 patients showed no difference in intrahospital mortality in those who receive prophylactic versus those receiving therapeutic doses of anticoagulant therapy (22.5% vs. 22.8%). The other two similar retrospective studies showed no differences in survival in patients on therapeutic versus those with prophylactic doses of anticoagulants. Another retrospective multicenter cohort study from the USA that included 3480 patients with COVID-19 disease showed a reduction in mortality at both therapeutic and prophylactic doses compared to those patients who did not receive thromboprophylaxis (22).

Clinically significant bleeding events are higher in those who received therapeutic doses compared to those with standard thromboprophylaxis doses. One US study found that 19 patients (0.5%) developed hemorrhagic stroke in those receiving a therapeutic dose of anticoagulant (89.5% of patients included in the study). Based on the available evidence, routine administration of therapeutic doses of anticoagulant therapy is not recommended. The benefit of therapeutic doses of anticoagulant therapy is currently controversial and further confirmation is needed based on retrospective studies (23).

The advantages of direct oral anticoagulants (DOAC) include facilitation of discharge planning and outpatient follow-up, as no laboratory monitoring is required.

DOACs have a longer half-life than UFH and LMWH, which can complicate urgent invasive procedures and the development of renal impairment. Caution should be exercised when using them in patients with impaired renal function, and other risks may include a potential effect on bioavailability and clinical efficacy due to interactions with other drugs, such as dexamethasone, which may reduce DOAC levels through P-gp induction and CYP3A4 induction enzymes in the liver (24).

One prospective study conducted in Italy included 844 COVID-19 patients taking DOAC before hospitalization. Patients with DOAC developed acute hypoxemic respiratory failure more frequently compared to patients who did not take DOAC and had a higher mortality rate (44.6% vs. 19.8%, P <0.001) (25).

A retrospective study conducted in the United States, analyzing 3625 patients with moderate or severe clinical condition of COVID-19 infection, showed that therapeutic anticoagulation involving apixaban had similar efficacy as enoxaparin in reducing mortality in hospitalized COVID-19 patients (26).

Following clinical improvement and when patient discharge is planned, clinically stable patients with VTE may be switched from low molecular weight heparin (LMWH) to DOAC or vitamin K antagonists with a treatment plan for at least 3 months in the absence of additional risk factors for thrombosis (24).

Ticagrelor, an inhibitor of the platelet receptor P2Y12, blocks platelet activation and aggregation, can be considered as an alternative to platelet prophylaxis. Ticagrelor can reduce lung damage during the development of pneumonia, reducing the levels of proinflammatory cytokines (IL-6, TNF-α, IL-8). Ticagrelor is only available as an oral therapeutic agent and its use is limited in patients on mechanical ventilation, where the use of Cangrelor, a similar P2Y12 inhibitor for intravenous administration, may be considered. There are no documented clinical studies in their efficacy and application in COVID-19 disease (22).

The safety and efficacy of aspirin for VTE prophylaxis remain unknown. In those with cardiovascular disease, a cohort study of 412 COVID-19 patients taking aspirin within 24 hours of hospital admission or 7 days before hospital admission found that its use was independently associated with a lower risk of mechanical ventilation, admission to units' intensive care and in-hospital mortality. Although a reduction in the rate of micro thrombosis would be the assumed mechanism of action, the benefit of aspirin remains to be seen in COVID-19 patients without cardiovascular disease (27).

Thrombolytic therapy is recommended in patients with proven pulmonary embolism (PE) and hemodynamic instability or signs of cardiogenic shock, who are not at high risk of bleeding. Peripheral thrombolysis is recommended prefer than catheter-guided thrombolysis in COVID-19 patients (28).

Several studies have identified laboratory models of stratification based on D-dimer thresholds to identify patients who should receive a prophylactic or therapeutic dose of anticoagulant, even with low clinical suspicion of VTE. Those with a D-di-

mer level consistently <1,000 μg / L should receive standard prophylactic doses, and those with an initial level <1,000 μg/L on admission, but with a significant increase during hospitalization to 2000-4000 μg / L, patient diagnosis for DVT or PE may be considered, especially for patients with clinically evident symptoms. When diagnostic procedures are not feasible and clinical suspicion of VTE is high, therapeutic doses of low molecular weight heparin (LMWH) are recommended, provided there is low risk of bleeding (29).

A large multicenter study conducted in the United States showed that serum D-dimer levels greater than 2600 ng/mL (reference values 0–292 ng/mL) represent a discriminant factor for the occurrence of VTE. One study conducted in France showed a predictive value for the development of PE with "cutoff" values of D-dimer greater than 2590 ng/ml and values of D dimer greater than 2590 ng/ml were associated with a 17-fold higher risk of PE occurrence. This supports the widespread use of D-dimer measurements as PE screening in hospitalized COVID-19 patients (30).

Conclusions

Prophylactic doses of low-molecular-weight (LMWH) or unfractionated (UFH) heparin are recommended to all hospitalized patients with COVID-19 infection. In hospitalized COVID-19 patients with a high clinical risk of developing venous thromboembolism (VTE) and D-dimer values greater than 2600 ng/ml, the use of therapeutic doses of LMWH in doses adjusted to the patient's body weight should be considered, in the absence of a higher risk of bleeding.

There is no conflict of interest.

References

1. D Atri, HK Siddiqi, J Lang, V Nauffal, DA Morrow, Bohula EA. COVID-19 for the cardiologist: a current review of the virology, clinical epidemiology, cardiac and other clinical manifestations and potential therapeutic strategies. JACC Basic Transl Sci. 2020; 518–536. https://doi.org/10.1016/j.jacbts.2020.04.002.
2. Terpos I, Ntanasis-Stathopoulos I, Elalamy E, Kastritis TN, Sergentanis M, Politou T, et al. Hematological findings and complications of COVID-19. Am. J. Hematol. 2020; 95: 834–847. https://doi.org/10.1002/ajh.25829.
3. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T 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. https://doi.org/ 10.1016/j.thromres.2020.04.024

4. Giannis IA, Ziogas P. Gianni. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J. Clin. Virol. 2020; 127: 104362. https://doi.org/10.1016/j.jcv.2020.104362.
5. 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(4): 844–847. https://doi.org/10.1111/jth.14768.
6. Thachil J. What do monitoring platelet counts in COVID-19 teach us? J. Thromb. Haemost. 2020; 18 (8): 2071–2072. https://doi.org/10.1111/jth.14879.
7. Fletcher-Sandersj O, Bellander BM. Is COVID-19 associated thrombosis caused by overactivation of the complement cascade? A literature review. Thromb. Res. 2020; 194: 36–41. https://doi.org/10.1016/j.thromres.2020.06.027.
8. B.M. Henry, J. Vikse, S. Benoit, E.J. Favaloro, G. Lippi. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin. Chim. Acta. 2020; 507: 167–173. https://doi.org/ 10.1016/j.cca.2020.04.027.
9. Gabrielli M, Lamendola P, Esperide A, Valletta F, Franceschi F. COVID-19 and thrombotic complications: pulmonary thrombosis rather than embolism? Thromb. Res. 2020; 193: 98. https://doi.org/10.1016/j.thromres.2020.06.014.
10. Gavriilaki E, Brodsky RA. Severe COVID-19 infection and thrombotic microangiopathy: success doesn't come easily. Br J Haematol. 2020; 189(6):227–230. https://doi.org/10.1111/bjh.16783.
11. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J. Thromb. Haemost. 2020; 18(6): 1324–1329. https://doi.org/10.1111/jth.14859.
12. Zuo Y, Warnock M, Harbaugh A, Yalavarthi S, Gockman K, Zuo M, et al. Plasma tissue plasminogen activator and plasminogen activator inhibitor-1 in hospitalized COVID19 patients. Scientific Reports. 2021; 11(1):1–9.
13. Iba T, Levy JH, Warkentin TE, Thachil J, T. van der Poll, Levi M. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J. Thromb. Haemost. 2019; 17(11): 1989–1994. https://doi.org/ 10.1111/jth.14578.
14. Seheult JN, Seshadri A, Neal MD. Fibrinolysis shutdown and thrombosis in severe COVID-19. J. Am. Coll. Surg. 2020; 231(2): 203–204. https://doi.org/ 10.1016/j.jamcollsurg.2020.05.021.
15. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu J, Shang Y. Thrombocytopenia and its association with mortality in patients with COVID-19. J. Thromb. Haemost. 2020; 18(6): 1469–1472. https://doi.org/10.1111/jth.14848.
16. Cheng R, Leedy D. COVID-19 and acute myocardial injury: the heart of the matter or an innocent bystander? Heart. 2020; 106: 1122–1124. https://doi.org/ 10.1136/heartjnl-2020-317025
17. Klok A, Kruip MJHA, N.J.M. van der Meer, Arbous MS, Gommers DAMPJ, Kant KM et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb. Res. 2020; 191: 145–147. https://doi.org/10.1016/j. thromres.2020.04.013

18. Middeldorp S, Coppens M, T.F. van Haaps, Foppen M, Vlaar AP, Müller M.C.A. et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J. Thromb. Haemost. 2020; 18 (8): 1995–2002. https://doi.org/10.1111/ jth.14888
19. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020; 18(5): 1023–1026.
20. Barnes GD, Burnett A, Allen A, Blumestein M, Clark N, Cuker P et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis*. 2020; 50(1): 72–81. https://www.ncbi.nlm.nih.gov/pubmed/32440883
21. Taccone FS, Gevenois PA, Peluso L, Pletchette Z, Lheureu O, Brasseur A et al. Higher intensity thromboprophylaxis regimens and pulmonary embolism in critically ill coronavirus disease 2019 patients. Crit Care Med. 2020; 48: e1087–e1090.
22. Longhitano Y, Racca F, Zanza C, Muncinelli M, Guagliano A, Peretti E et al. Venous thrombo-embolism in hospitalized SARS-CoV-2 patients treated with three different anticoagulation protocols: prospective observational study. Biology. 2020; 9 (10): 310.
23. Paranjpe I, Fuster V, LalaA, Russak AJ, Glicksberg BS, Levin MA et al.Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020; 76 (1): 122–124.
24. Kartsios C, Lokare A, Osman H, Perrin D, Razaq S, Ayub N et al. Diagnosis, management, and outcomes of venous thromboembolism in COVID-19 positive patients: a role for direct anticoagulants? J Thromb Thrombolysis. 2021; 51(4): 947–952. https://doi.org/10.1007/s11239-020-02257-7.
25. Schiavone M, Gasperett A, Mancone M, Curni A, Mascioli G, Mitacchione G, et al.Oral anticoagulation and clinical outcomes in COVID-19: an Italian multicenter experience. Int J Cardiol. 2021; 323: 276–280.
26. Billett H, Reyes G, Szymanski M, Ikemura J, Stahl KL, Lo Y, et al. Anticoagulation in COVID-19: effect of enoxaparin, heparin, and apixaban on mortality. Thromb Haemost. 2020; 120: 1691–1699.
27. Rosovsky RP, Sanfilippo KM., Wang TF, Rajan SK, Shah S, Martin KA, et al. Anticoagulation practice patterns in COVID-19: a global survey. Res Pract Thromb Haemost. 2020; 4(6): 969–983.
28. larcon-Calderon A, Celli D, Plate T, Galo J, Alvarez R. Massive pulmonary embolism treated with thrombolysis in COVID-19: a case series. Chest. 2020; 158 (4): A2126–A2127.
29. Flaczyk A, Rosovsky RP, Reed CT, Bankhead,Kendall BK, Bittner EA, Chang MG. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations. Crit Care. 2020; 24 (1): 1–13.
30. Spyropoulos AC, LipardiC, Xu J, Peluso C, Spiro TE, De Sanctis Y, et al. Modified IMPROVE VTE risk score and elevated D-dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *TH Open*. 2020; 4(1): e59–e65.