

COVID-19: coagulation disorders and anticoagulant treatment in patients hospitalised in ICU

Jan Pluta, Agnieszka Cieniewicz, Janusz Trzebicki

1st Department of Anaesthesiology and Intensive Care, Medical University of Warsaw, Poland

Abstract

Patients hospitalized in the intensive care unit (ICU) due to the COVID-19 experience a high incidence (up to 43%) of venous thromboembolic events. While laboratory findings in COVID-19-associated coagulopathy (CAC) show increased D-dimer and fibrinogen levels, the abnormalities in standard coagulation tests and platelet count are minimal. Recent studies suggest contribution of fibrinolysis shutdown to this phenomenon. Endothelial injury and alteration of its antithrombotic activity can lead to micro- and macrovascular thrombosis in the lungs, occurrence of which is associated with poor clinical outcome in critically ill patients with COVID-19.

Additionally, the hypercoagulability induced by activation of coagulation pathways during the immune response to SARS-CoV-2 infection contributes to impaired organ perfusion. This, alongside with hypoxemia, leads to multiorgan failure.

Various diagnostic regimens, some of which include global assays of haemostasis, are currently being published and discussed. Numerous guidelines and recommendations of scientific societies and groups of specialists have been published. However, there is no single optimal algorithm for anticoagulation treatment and monitoring specific to the ICU patients with COVID-19. The authors have attempted to summarize the data related to CAC and thrombotic disease and develop an algorithm consistent with the latest clinical practice guideline recommendations.

Key words: heparin, thromboelastometry, COVID-19, SARS-CoV-2, CAC, anty-Xa, thrombosis, coagulopathy, anticoagulation, fibrinolysis.

Anaesthesiol Intensive Ther 2021;53,2: 153–161

Received: 14.12.2020, accepted: 07.04.2021

CORRESPONDING AUTHOR:

Jan Pluta, 1st Department of Anaesthesiology and Intensive Care, Medical University of Warsaw, 4 Lindleya St., 02-005 Warsaw, Poland, e-mail: jan.pluta@wum.edu.pl

The issues related to haemostatic disorders and their treatment are being widely discussed in the literature concerning the diagnosis and management of patients diagnosed with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1–3]. The findings of numerous worldwide studies have demonstrated that the haemostatic system is one of the most important systems substantially impaired by the viral infection, which can result in serious life-threatening complications [4–6]. It is already known that hypercoagulation [7, 8] is the dominant coagulopathy in patients infected with SARS-CoV-2. Its consequences in the form of blood clots and emboli in the blood vessels of various organs in combination with thrombocytopenia lead to severe disorders of haemostasis in some patients and require ICU treatment [9–11]. According to the literature data, the incidence of thromboembolic incidents in this group of patients reaches 43% and increases with the length of hospitalization [12, 13]. The incidence of pulmonary embolism, which is observed most frequently, is six-fold higher in patients

with COVID-19-associated acute respiratory distress syndrome (ARDS), as compared to patients with ARDS of some different aetiology [14]. Therefore, optimal diagnosis of haemostatic disorders and effective treatment of coagulopathy are the elements of therapeutic management, which can improve the prognosis in most critically ill patients.

The aim of the paper was to synthesise information on the diagnosis and therapy of haemostatic disorders in patients infected with SARS-CoV-2 requiring intensive care. The authors did not present their own recommendations or guidelines, but merely attempted to summarise the existing knowledge on the subject in an orderly manner.

EPIDEMIOLOGY OF COVID-19 IN POLAND AND WORLDWIDE

In March 2020, the World Health Organization declared COVID-19 a pandemic caused by a new type of coronavirus: SARS-CoV-2. During the infection, patients develop pneumonia, the main symptoms of which are fever, dry cough, and progressive

shortness of breath. The first reports of pneumonia cases emerged from the Chinese City of Wuhan, Hubei Province, in December 2019. In Poland, the first case was confirmed on March 4, 2020 in an individual returning from abroad. At the beginning of December 2020, the number of infections worldwide exceeded 66 million and more than 1.5 million people died; in Poland, the number of infections exceeded one million cases and 19 thousand deaths were reported [15].

PATHOPHYSIOLOGY AND PATHOMORPHOLOGY

In the pathogenesis of thromboembolic complications in COVID-19, all elements of the Virchow's triad are involved: endothelial damage, coagulation disorders and blood flow abnormalities.

The invasion of SARS-CoV-2 into the endothelial cells leads to their activation, which initiates local inflammation. This promotes increased vascular permeability while disturbed production of nitric oxide and prostacyclin I impairs their antithrombotic properties. Upon activation, neutrophils can release neutrophil extracellular traps (NETs), which may promote thrombosis [16]. Moreover, endothelial activation results in enhanced expression of plasminogen activator inhibitor-1 (PAI-1), tissue factor (TF) and release of von Willebrand factor (vWF). The activity of thrombomodulin and tissue plasminogen activator (t-PA) decreases [17]. The third element of Virchow's triad is abnormal blood flow. In ICU patients, this abnormal flow is caused by immobilization and angiopathies resulting from the exacerbation of chronic cardiovascular diseases, diabetes, renal failure, and age-related fragility.

The problems associated with impaired organ perfusion resulting from the presence of thromboembolic lesions have been described by Shah *et al.* [12]. In their study group, numerous thromboembolic complications have been observed, such as strokes, myocardial infarction, and ischaemic intestinal lesions. The authors have also reported extra-

corporeal circuit thrombosis in more than 12% of patients.

Anatomopathological studies of the lungs of patients who died of COVID-19 have shown massive endothelial damage and diffuse alveolar damage (DAD) in 67% of subjects [18]. Intra-alveolar fibrin deposition and the presence of vitreous membranes have been observed. Diffuse thrombotic lesions and microthrombi in the pulmonary capillaries have also been found, whose incidence was 9 times higher than in patients with influenza virus infection [10]. Furthermore, microthrombi have been detected in the arteries 1–2 mm in diameter, without complete occlusion of their lumen. The above histological findings have been confirmed by microtomographic (micro-CT 3D) studies of the lungs, which demonstrate almost complete obstruction of pre- and post-capillary vessels. Moreover, increased angiogenesis has been observed and its incidence was almost three-fold higher, as compared to patients with influenza. In autopsy studies, Wichmann *et al.* [18] have found deep vein thrombosis in 58% of patients. Pulmonary embolism was the direct cause of death of 1/3 of patients in the studied group. Features of disseminated intravascular coagulation (DIC) and small fibrin clots have been demonstrated in the renal glomeruli of COVID-19 patients [19].

CHARACTERISTICS OF COVID-19-ASSOCIATED COAGULOPATHY

COVID-19-associated coagulopathy (CAC) is characterised by hypercoagulation [20], which is a significant factor worsening prognosis [3].

Laboratory tests in CAC demonstrate a slight increase in prothrombin time (PT) and activated partial thromboplastin time (APTT), high D-dimer levels and elevated levels of fibrinogen, factor VIII and vWF [21].

The coagulation disorders described in CAC differ from those in coagulopathies commonly occurring in ICUs, such as DIC or sepsis-induced coagulopathy (SIC). The characteristics of these three types of coagulopathy and the scales enabling their description were presented in the updated recommendations of the Agency for Health Technology Assessment and Tariffication (AHTAT) of 27.11.2020 [22]. The main differentiating features of CAC and DIC were described in Table 1.

Coagulation tests

D-dimer

Increased D-dimer levels are observed during COVID-19 infection. Han *et al.* [23] have found higher D-dimer values in the study group of 94 patients with confirmed SARS-CoV-2 infection, as compared to the control group of 40 healthy volunteers. They

TABLE 1. Characteristics of COVID-19-associated coagulopathy (CAC) and disseminated intravascular coagulation (DIC)

Factor	CAC	DIC
Dominant picture of coagulopathy	Thrombosis	Haemorrhage
D-dimer	↑	↑
Fibrinogen	↑	↓
Platelets	↓/N	↓
PT	N/↑	↑
APTT	N/↑	↑
Fibrinolysis	↓	↑

↑ – result exceeding normal or range of reference values, ↓ – result below normal or range of reference values, N – result within normal limits or range of reference values, PT – prothrombin time, APTT – activated partial thromboplastin time

also observed that higher values correlated with a heavier course of COVID-19. This also applies to critically ill patients hospitalized in ICUs. High D-dimer values are one of the factors worsening the prognosis in COVID-19 [9]. The above observation has been confirmed by Tang *et al.* [3], who have found significantly higher values of this marker in non-survivors. A prospective observational study on the Polish population of patients treated in ICUs has demonstrated significantly higher D-dimer levels in patients who developed acute respiratory failure with $\text{PaO}_2/\text{FiO}_2 \leq 300$ mm Hg, as compared to those who did not meet the criteria of the Berlin definition of ARDS [24].

The literature reports different D-dimer cut-off values above which the risk of death increases significantly. For instance, ≥ 2000 ng mL⁻¹ according to Shang *et al.* [25] or a two times lower value according to Shou *et al.* [9]. In the AHTAT recommendations, a 6-fold increase in D-dimer above the upper limit of normal (500 ng mL⁻¹), i.e. 3000 ng mL⁻¹, is considered relevant [22].

Fibrinogen

Fibrinogen is a coagulation factor that is involved in the final phase of clot formation after transformation into fibrin and binding to the platelets to form the final clot stabilized by factor XIII. At the same time, it is an acute phase protein produced in the liver; therefore, its serum concentration significantly increases during inflammatory processes [26]. High concentrations of fibrinogen are one of the factors worsening the prognosis in COVID-19 due to a high risk of exacerbated thromboembolic complications [27]. On the other hand, significantly reduced fibrinogen concentrations have been observed in critically ill patients in whom this coagulation factor was substantially used in the final stage of the disease, most likely due to DIC [3].

Platelets

In COVID-19 infections, both thrombocytopenia and normal platelet counts are observed. In a meta-analysis conducted by Lippi *et al.* [28], low platelet counts have been found in patients with more severe infections. In a retrospective study involving 191 patients with COVID-19, Shou *et al.* [9] have found significantly lower platelet counts in non-survivors, as compared to survivors. Despite this difference, the number of thrombocytes in both groups did not differ significantly from the reference values, and severe thrombocytopenia occurred sporadically.

Liu *et al.* [29] have confirmed the importance of reduced thrombocyte counts as an independent risk factor for death in severe COVID-19 cases. According to them, thrombocytopenia was associ-

ated with a 3-fold higher risk of death compared to patients with normal platelet counts. A 50 G L⁻¹ increase in platelet counts was associated with a 40% reduction in the risk of death.

Coagulation times

The coagulation tests in the group of further 183 patients admitted to hospital with SARS-CoV-2 have shown normal or slightly prolonged coagulation times. Prolonged PT was observed more frequently in patients hospitalized in ICUs and in non-survivors [3]. This observation has been confirmed by a subsequent meta-analysis involving 6,320 patients with COVID-19. Prolongation of PT and more frequently reported APTT within the reference values may indicate that haemostatic disorders in SARS-CoV-2 infections are mainly associated with the extrinsic coagulation pathway [30].

Global tests of haemostasis

Thromboelastometry (ROTEM) and thromboelastography (TEG) are the diagnostic methods known as global tests of haemostasis (GTH). They enable quick and bedside assessment of the dynamics of formation, physical properties and lysis of a blood clot. Moreover, GTH findings allow to diagnose hypercoagulation and fibrinolysis, which is not possible in standard coagulation tests [31]. However, there are no explicit study results indicating that these methods should be routinely used for monitoring the anticoagulation therapy in patients with COVID-19.

Global tests of haemostasis – abnormal clot formation

In ROTEM studies performed in patients with SARS-CoV-2, Spiezia *et al.* [32] have demonstrated reduced times of clot formation and higher maximum clot firmness (MCF), indicative of a hypercoagulable state. Similar observations have been reported by Almskog *et al.* [33] in their prospective observational study with the control group of healthy individuals. Likewise, Pavoni *et al.* [34], who studied critically ill patients with COVID-19 hospitalised in ICUs, have found that ROTEM results indicated increased coagulation in more than 50% of patients. The above studies evidence that GTH can be used during the SARS-CoV-2 pandemic as a diagnostic tool to quickly identify patients with coagulopathy that increases the risk of thromboembolic complications.

Global tests of haemostasis – abnormal fibrinolysis, suppressed fibrinolysis

A disorder of fibrinolysis, particularly suppressed fibrinolysis, is a risk factor for thrombotic complications, multiple organ failure and increased mor-

tality [35–37]. Therefore, the effects of this phenomenon on haemostasis disorders in patients with COVID-19 are being studied. Tang *et al.* [3] have described the coagulation disorders in 449 patients with severe COVID-19 and concluded that suppressed fibrinolysis together with excessive thrombin generation may be the cause of hypercoagulation. Furthermore, on TEG testing, Wright *et al.* [38] have observed a complete lack of lysis at 30 minutes in 57% of patients with COVID-19, suggestive of suppressed fibrinolysis. Similar findings have been reported by Bakchoul *et al.* [39].

Further studies should evaluate the activators and inhibitors of fibrinolysis and plasmin-antiplasmin complexes to fully characterize the dynamics of fibrinolysis in patients with COVID-19. This may enable to assess more comprehensively whether the fibrinolysis disorders demonstrated in GTH are confirmed by the activity of proteins involved in this process and which of its elements has a significant effect on its occurrence.

Anticoagulant therapy in COVID-19 patients treated in ICU

There is a consensus on an increased risk of thromboembolic events in patients with COVID-19, which concerns 20–43% of those treated in ICUs. Such events occur mainly in the form of vein thrombosis of the lower extremities and pulmonary embolism, even in the presence of anticoagulant prophylaxis [40, 41]. Therefore, clinical trials are underway in many centres around the world to determine the most optimal anticoagulation regimen.

Choosing the optimal form of anticoagulation

The recommendations and guidelines with a wide impact can be found in the publications prepared by the International Society for Thrombosis and Haemostasis (ISTH), National Institutes of Health (NIH), Anticoagulation Forum (ACF), American Society of Hematology (ASH), American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC) [42–47]. The analysis of the above documents reveals that there is no single, universal, widely accepted and recommended algorithm of anticoagulant therapy. Based on them, however, the key clinical issues can be identified to minimise the risk of thromboembolic complications during ICU treatment of COVID-19 patients.

They include:

- determination of the optimal dose of anticoagulant therapy (prophylactic, intermediate or therapeutic dose),
- determination of the most beneficial route of administration (subcutaneous delivery or continuous intravenous infusion),

- determination of the factors affecting the need to modify the dose,
- determination of the most effective method for monitoring the treatment with heparins.

It is common practice in anticoagulant management of patients hospitalised in ICUs to use prophylactic doses of low-molecular-weight heparins (LMWHs).

The generally accepted contraindications for this kind of management are severe thrombocytopaenia ($< 25 \text{ G L}^{-1}$), active bleeding or a high risk of bleeding at the platelet count $< 50 \text{ G L}^{-1}$ [47–49].

In the ASH and AHA guidelines for the general population of critically ill patients, there is a strong recommendation for the use of LMWHs, which are preferred over unfractionated heparins (UFHs) and for mechanical forms of thromboprophylaxis [50, 51]. This has been confirmed by the results of the 2011 PROTECT study, demonstrating that patients receiving LMWHs have fewer pulmonary embolism incidents than the UFH group. However, no differences in the incidence of deep vein thrombosis have been found [52].

Tang *et al.* [53] have confirmed the efficacy of LMWHs in COVID-19 patients with high levels of D-dimer (≥ 6 times the upper limit of normal) or the SIC score ≥ 4 . These patients were characterised by lower 28-day mortality, as compared to patients without thromboprophylaxis.

On April 21, 2020, the ESC presented its statement on the care of patients with cardiac conditions during the pandemic. In cases of acute pulmonary embolism, the existing guidelines should be followed. As far as COVID-19 patients are concerned, the lack of significant interactions between heparins and drugs used in experimental therapies is highlighted. Caution is recommended when non-vitamin K antagonist oral anticoagulants (NOACs) are used. Interactions with some specific antiviral agents (i.e. lopinavir and ritonavir) that increase the risk of bleeding are possible [54, 55]. Therefore, the vast majority of guidelines do not recommend the use of NOACs in these patients in ICUs; instead, the therapy with heparins is advocated. As recommended by ISTH, NOAC therapy should be considered after discharge from the ICU [47].

The only document in force in Poland providing comprehensive diagnostic and therapeutic recommendations for the care of patients with COVID-19, which was commissioned by the Minister of Health, is the guidelines of the Agency for Medical Technology Assessment and Tariffication (AHTAT) of 25.04.2020. The part on prophylactic anticoagulation recommends the routine use of heparins in prophylactic doses in all severely ill patients [56]. The document was updated on November 27, 2020 [22].

According to the comparative analysis of the European and American guidelines and recommendations published in Critical Care by Flaczyk *et al.* [57], the following should be considered to determine detailed indications and to optimise heparin dosages in anticoagulant prophylaxis in COVID-19 patients:

- kidney function,
- body weight,
- platelet count,
- fibrinogen concentration,
- APTT and anti-Xa results.

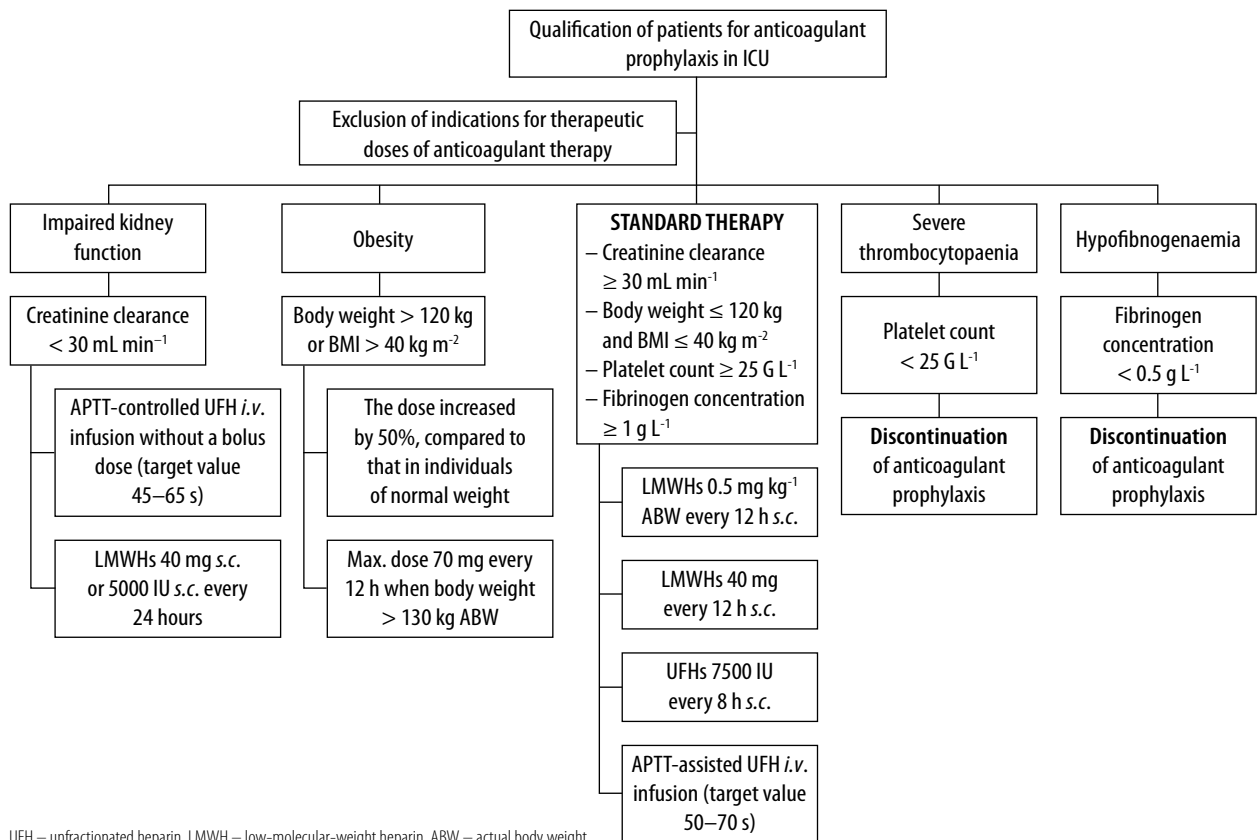
The above-mentioned analysis and updated AHTAT recommendations introduce the term of the intermediate dose of low-molecular-weight heparin. Despite an increased risk of thromboembolic complications, the routine use of therapeutic doses of heparins for anticoagulant prophylaxis is not recommended. The risks associated with higher doses of LMWHs are also highlighted by Longhitano *et al.* [58]. In a prospective observational study involving 74 patients, the authors have not observed reduced incidences of thromboembolic episodes in patients receiving intermediate and therapeutic doses; however, they have found higher incidences of severe haemorrhagic complications in this group of patients. High incidences of thromboembolic events despite the use of therapeutic doses have also been

demonstrated by Llitjos *et al.* [8]. However, the number of complications reported was significantly lower than in the group receiving prophylactic doses of LMWHs. The most conservative approach has been presented by the NIH, which allows any changes to the standard anticoagulation regimen only during clinical trials [59].

The synthesis of the above recommendations was graphically shown in Figure 1 [43, 46, 48, 57, 60].

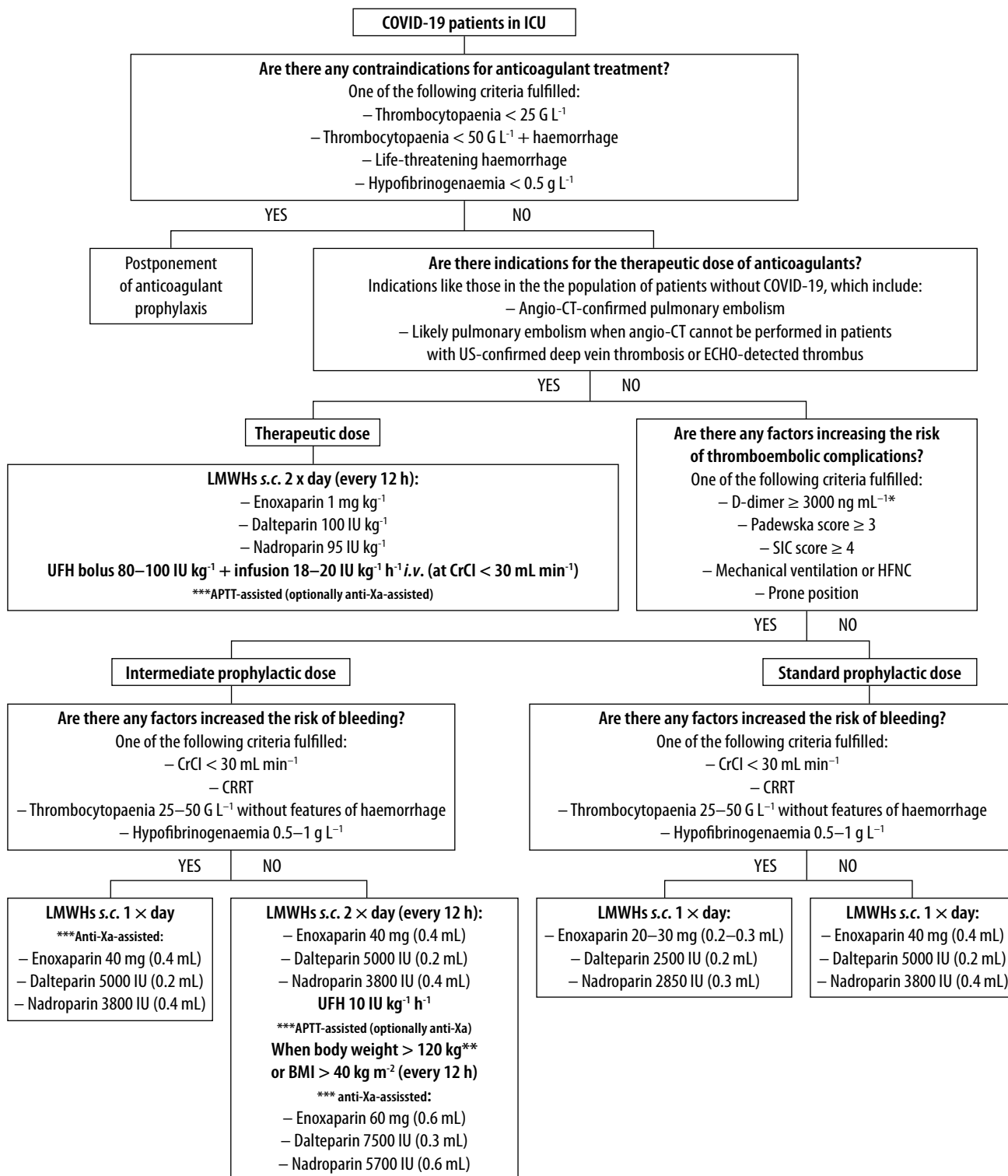
In November 2020, the recommendations for the care of COVID-19 patients requiring hospitalisation were published on the Ministry of Health's Website as part of Strategy 3.0 [61]. In the section on anticoagulant prophylaxis and treatment, the authors confirm that intermediate doses of LMWHs are appropriate for patients with severe COVID-19 with D-dimer concentrations of $\geq 1500 \text{ ng mL}^{-1}$ and a Padua score of ≥ 3 points. Higher doses of LMWHs should be considered for obese patients. However, there are no detailed data concerning the adaption of anticoagulant therapy in cases of acute renal failure requiring continuous renal replacement therapy, thrombocytopenia or extreme body weight, which are common in ICUs.

Based on the information found in Polish and international recommendations and guidelines, supplemented by the latest recommendations of the AHTAT of 27 November 2020, the authors sug-



UFH – unfractionated heparin, LMWH – low-molecular-weight heparin, ABW – actual body weight

FIGURE 1. Recommended modifications of anticoagulant prophylaxis in ICU depending on the clinical situation (based on [43, 46, 48, 57, 60])



*According to the predominant opinion, D-dimer concentration 6 times higher the upper limit of normal (500 ng mL⁻¹), which corresponds to 3000 ng mL⁻¹

**The majority of recommendations stress the difficulties in determining the precise dosing in patients with extreme body weight (< 50 kg or > 120 kg). The solution suggested in literature based on some simplification is to use enoxaparin 0.5 mg kg⁻¹

*****MONITORING OF HEPARIN DOSES (target values printed in bold):**

LMWHs:

- Anti-Xa for intermediate doses: **0.3–0.7 IU mL** (3–4 h after the dose, minimum after the third dose)
- Anti-Xa for therapeutic doses: **0.5–1 IU mL** (3–4 h after the dose, minimum after the third dose)

UFHs:

- Anti-Xa for intermediate doses: **0.3–0.5 IU mL**
- Anti-Xa for therapeutic doses: **0.5–0.7 IU mL**
- APTT: **50–70 seconds**, at CrCl < 30 mL min⁻¹: **45–65 seconds**

The final ranges of target values should be consulted with a local laboratory!

SIC – sepsis-induced coagulopathy, HFNC – high-flow nasal oxygen, CrCl – creatinine clearance, CRRT – continuous renal replacement therapy, APTT – activated partial thromboplastin time

FIGURE 2. Anticoagulant management algorithm in COVID-19 patients treated in ICU (based on [22, 57, 62, 63]).

gest the following anticoagulant regimen in patients with COVID-19 treated in ICUs (Figure 2) [22, 57, 62, 63].

Monitoring of anticoagulant therapy (APTT, anti-Xa)

The commonly accepted practice is to determine the APTT in patients treated with UFH infusions. This form of anticoagulant therapy is particularly recommended in COVID-19 patients with a high risk of prothrombotic complications, end-stage renal failure and obesity [63].

Standard anticoagulant prophylaxis with LMWHs does not require routine monitoring. On the other hand, the use of intermediate and therapeutic doses, particularly in patients with extreme body weight, when there is an increased risk of bleeding, haematological disorders or suspected heparin resistance, should be monitored [62, 64].

The optimal method for assessing the effectiveness of LMWH therapy is anti-Xa testing [65, 66], which enables highly desirable individualisation of anticoagulant therapy; such individualisation is particularly important in anticoagulant management of COVID-19 patients. However, an adequate range of anti-X values may prove to be an important issue in clinical practice. Based on the results in the group of COVID-19 patients receiving LMWH thromboprophylaxis, Dutt *et al.* [67] have demonstrated low anti-Xa activity ($< 0.1 \text{ IU mL}^{-1}$) in 95% of patients treated in ICUs compared with 27% of patients not requiring intensive care. In view of the above, some authors indicate that determinations of anti-Xa activity are also grounded when prophylactic doses are used in COVID-19 patients, with a target value of $0.2\text{--}0.4/0.5 \text{ IU mL}^{-1}$ [68]. Due to the reports demonstrating insufficient anti-Xa activity when prophylactic doses are used, higher (intermediate or therapeutic) doses of heparins have been considered to achieve the expected anti-Xa values in COVID-19 patients treated in ICUs [13, 41].

Antiplatelet therapy

According to the management regimen in some centres, LMWH or UFH treatment should be supplemented with antiplatelet drugs, the most common of which is acetylsalicylic acid.

The results of a retrospective analysis carried out by Chow *et al.* [69] in a group of 412 patients, have demonstrated that the use of ASA reduces the need for mechanical ventilation, the number of ICU admissions and intra-hospital mortality. However, it does not affect the incidence of severe haemorrhages and thromboembolic episodes.

At present, the guidelines and recommendations do not advocate routine antiplatelet therapy

unless it has been chronically used before hospitalisation due to COVID-19 [22, 59].

CONCLUSIONS

The current findings on COVID-19 indicate that the disease is strongly associated with haemostasis disorders, resulting in hypercoagulation. The clinical picture of this coagulopathy in the form of respiratory failure and frequent dysfunctions of other systems is the result of micro- and macro-emboli. In this context, the implementation of optimal prevention or anticoagulant treatment is essential for the care of COVID-19 patients. Patients infected with SARS-CoV-2 with extreme body weight or hospitalized in ICUs require special attention during prevention or treatment with heparins. The above synthesis of information from current guidelines and recommendations allows to conclude that LMWH doses should be individualised in these groups of patients considering the results of anti-Xa activity monitoring; when UFHs are used, anti-Xa or APTT should be determined. However, the knowledge of all pathophysiological processes resulting from SARS-CoV-2 infection and the host immune response is incomplete and requires further research. We hope that the heparin dosing algorithm for ICU patients presented by us and based on the most up-to-date information will prove useful for optimizing anticoagulant therapy.

Acknowledgements

1. The authors would like to thank Prof. Piotr Pruszczyk, Head of the Department of Internal Diseases and Cardiology, Centre for Management of Venous Thromboembolic Disease, Medical University of Warsaw, for substantive support and critical assessment.
2. Financial support and sponsorship: none.
3. Conflict of interest: none.

REFERENCES

1. Liu Y, Gao W, Guo W, et al. Prominent coagulation disorder is closely related to inflammatory response and could be as a prognostic indicator for ICU patients with COVID-19. *J Thromb Thrombolysis* 2020; 50: 825-832. doi: <https://doi.org/10.1007/s11239-020-02174-9>.
2. Görlinger K, Dirkmann D, Gandhi A, Simioni P. COVID-19-associated coagulopathy and inflammatory response: what do we know already and what are the knowledge gaps? *Anesth Analg* 2020; 131: 1324-1333. doi: <https://doi.org/10.1213/ANE.00000000000005147>.
3. 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. doi: <https://doi.org/10.1111/jth.14768>.
4. Jin S, Jin Y, Xu B, Hong J, Yang X. Prevalence and impact of coagulation dysfunction in COVID-19 in China: a meta-analysis. *Thromb Haemost* 2020; 120: 1524-1535. <https://doi.org/10.1055/s-0040-1714369>.
5. Hasan SS, Radford S, Kow CS, Zaidi STR. Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis.

- J Thromb Thrombolysis 2020; 50: 814-821. doi: <https://doi.org/10.1007/s11239-020-02235-z>.
6. Ranucci M, Sitzia C, Baryshnikova E, et al. Covid-19-associated coagulopathy: biomarkers of thrombin generation and fibrinolysis leading the outcome. *J Clin Med* 2020; 9: 3487. doi: <https://doi.org/10.3390/jcm9113487>.
 7. Thachil J, Juffermans NP, Ranucci M, et al. ISTH DIC subcommittee communication on anticoagulation in COVID-19. *J Thromb Haemost* 2020; 18: 2138-2144. doi: <https://doi.org/10.1111/jth.15004>.
 8. Litijos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020; 18: 1743-1746. doi: <https://doi.org/10.1111/jth.14869>.
 9. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054-1062. doi: [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
 10. 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. doi: <https://doi.org/10.1056/nejmoa2015432>.
 11. Rahi MS, Jindal V, Reyes SP, Gunasekaran K, Gupta R, Jaiyesimi I. Hematologic disorders associated with COVID-19: a review. *Ann Hematol* 2021; 100: 309-320. doi: <https://doi.org/10.1007/s00277-020-04366-y>.
 12. Shah A, Donovan K, McHugh A, et al. Thrombotic and haemorrhagic complications in critically ill patients with COVID-19: a multicentre observational study. *Crit Care* 2020; 24: 561. doi: <https://doi.org/10.1186/s13054-020-03260-3>.
 13. 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. doi: <https://doi.org/10.1016/j.thromres.2020.04.013>.
 14. 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. doi: <https://doi.org/10.1007/s00134-020-06062-x>.
 15. Johns Hopkins University of Medicine. The Johns Hopkins Coronavirus Resource Center 2020. Available at: <https://coronavirus.jhu.edu/> (Accessed: 05.12.2020).
 16. Zuo Y, Zuo M, Yalavarthi S, et al. Neutrophil extracellular traps and thrombosis in COVID-19. *J Thromb Thrombolysis* 2021; 51: 446-453. doi: <https://doi.org/10.1007/s11239-020-02324-z>.
 17. Siddiqi HK, Libby P, Ridker PM. COVID-19 – a vascular disease. *Trends Cardiovasc Med* 2021; 31: 1-5. doi: <https://doi.org/10.1016/j.tcm.2020.10.005>.
 18. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020; 173: 268-277. doi: <https://doi.org/10.7326/M20-2003>.
 19. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology* 2020; 77: 198-209. doi: <https://doi.org/10.1111/his.14134>.
 20. Abou-Ismaïl MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res* 2020; 194: 101-115. doi: <https://doi.org/10.1016/j.thromres.2020.06.029>.
 21. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost* 2020; 18: 1738-1742. doi: <https://doi.org/10.1111/jth.14850>.
 22. Agencja Oceny Technologii Medycznych i Taryfikacji. Farmakoterapia COVID-19 – Aktualizacja (Wersja 2.0). 27.11.2020. Available at: https://www.aotm.gov.pl/media/2020/12/Farmakoterapia-COVID-19-Aktualizacja-wersja-2.0-27-listopada-2020-r._new_aktualna.pdf (Accessed: 22.02.2021).
 23. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 2020; 58: 1116-1120. doi: <https://doi.org/10.1515/cclm-2020-0188>.
 24. Piwowarczyk P, Szczukocka M, Kutnik P, et al. Risk factors and outcomes for acute respiratory failure in coronavirus disease 2019: an observational cohort study. *Adv Clin Exp Med* 2021; 30: 165-171. doi: <https://doi.org/10.17219/ACEM/130603>.
 25. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost* 2020; 18: 1324-1329. doi: <https://doi.org/10.1111/jth.14859>.
 26. Davalos D, Akassoglou K. Fibrinogen as a key regulator of inflammation in disease. *Semin Immunopathol* 2012; 34: 43-62. doi: <https://doi.org/10.1007/s00281-011-0290-8>.
 27. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. *Crit Care Med* 2020; 1358-1364. doi: <https://doi.org/10.1097/CCM.0000000000004458>.
 28. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020; 506: 145-148. doi: <https://doi.org/10.1016/j.cca.2020.03.022>.
 29. Liu Y, Sun W, Guo Y, et al. Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study. *Platelets* 2020; 31: 490-496. doi: <https://doi.org/10.1080/09537104.2020.1754383>.
 30. Elshazli RM, Toraih EA, Elgaml A, et al. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: a meta-analysis of 6320 patients. *PLoS One* 2020; 15: e0238160. doi: <https://doi.org/10.1371/journal.pone.0238160>.
 31. Trzebicki J, Kuzmińska G, Domagała P. Tromboelastometria – nowa metoda wspomagająca decyzje terapeutyczne w zaburzeniach hemostazy, oparta na tromboelastografii Harteta. *Pol Merkur Lekarski* 2009; 27: 85-91.
 32. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thromb Haemost* 2020; 120: 998-1000. doi: <https://doi.org/10.1055/s-0040-1710018>.
 33. Almskog LM, Wikman A, Svensson J, et al. Rotational thromboelastometry results are associated with care level in COVID-19. *J Thromb Thrombolysis* 2021; 51: 437-445. doi: <https://doi.org/10.1007/s11239-020-02312-3>.
 34. Pavoni V, Giancesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. *J Thromb Thrombolysis* 2020; 50: 281-286. doi: <https://doi.org/10.1007/s11239-020-02130-7>.
 35. Schmitt FCF, Manolov V, Morgenstern J, et al. Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: results of an observational pilot study. *Ann Intensive Care* 2019; 9: 19. doi: <https://doi.org/10.1186/s13613-019-0499-6>.
 36. Moore HB, Moore EE, Neal MD, et al. Fibrinolysis shutdown in trauma. *Anesth Analg* 2019; 129: 762-773. doi: <https://doi.org/10.1213/ANE.0000000000004234>.
 37. Gomez-Builes JC, Acuna SA, Nascimento B, Madotto F, Rizoli SB. Harmful or physiologic: diagnosing fibrinolysis shutdown in a trauma cohort with rotational thromboelastometry. *Anesth Analg* 2018; 127: 840-849. doi: <https://doi.org/10.1213/ANE.0000000000003341>.
 38. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. *J Am Coll Surg* 2020; 231: 193-203.e1. doi: <https://doi.org/10.1016/j.jamcollsurg.2020.05.007>.
 39. Bakchoul T, Hammer S, Lang P, Rosenberger P. Fibrinolysis shutdown in COVID-19 patients: report on two severe cases with potential diagnostic and clinical relevance. *Thromb Updat* 2020; 1: 100008. doi: <https://doi.org/10.1016/j.tru.2020.100008>.
 40. Lodigiani C, Iapichino G, Carenzo L, 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. doi: <https://doi.org/10.1016/j.thromres.2020.04.024>.
 41. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020; 18: 1995-2002. doi: <https://doi.org/10.1111/jth.14888>.
 42. National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) treatment guidelines. Available at: <https://www.covid19treatmentguidelines.nih.gov/> (Accessed: 22.02.2021).
 43. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis* 2020; 50: 72-81. doi: <https://doi.org/10.1007/s11239-020-02138-z>.
 44. Cuker A, Tseng EK, Nieuwlaar R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv* 2021; 5: 872-888. doi: <https://doi.org/10.1182/bloodadvances.202003763>.
 45. Ortega-Paz L, Capodanno D, Montalescot G, Angiolillo DJ. Coronavirus disease 2019-associated thrombosis and coagulopathy: review of the pathophysiological characteristics and implications for anti-

- thrombotic management. *J Am Heart Assoc* 2021; 10: e019650. doi: <https://doi.org/10.1161/JAHA.120.019650>.
46. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol* 2020; 75: 2950-2973. doi: <https://doi.org/10.1016/j.jacc.2020.04.031>.
 47. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020; 18: 1859-1865. doi: <https://doi.org/10.1111/jth.14929>.
 48. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020; 18: 1023-1026. doi: <https://doi.org/10.1111/jth.14810>.
 49. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. *Chest* 2020; 158: 1143-1163. doi: <https://doi.org/10.1016/j.chest.2020.05.559>.
 50. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv* 2018; 2: 3198-3225. doi: <https://doi.org/10.1182/bloodadvances.2018022954>.
 51. Cushman M, Barnes GD, Creager MA, et al. Venous thromboembolism research priorities: a scientific statement from the American heart association and the international society on thrombosis and haemostasis. *Circulation* 2020; 142: E85-E94. doi: <https://doi.org/10.1161/CIR.0000000000000818>.
 52. The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 2011; 364: 1305-1314. doi: <https://doi.org/10.1056/nejmoa1014475>.
 53. 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. doi: <https://doi.org/10.1111/jth.14817>.
 54. Sokolski M, Sokolska JM, Ponikowski P, et al. Choroby układu sercowo-naczyniowego w czasie pandemii COVID-19 w świetle aktualnych danych naukowych oraz stanowisk European Society of Cardiology i European Society of Hypertension. *Med Prakt* 2020; 5: 12-44.
 55. Vivas D, Roldán V, Esteve-Pastor MA, et al. Recommendations on antithrombotic treatment during the COVID-19 pandemic. Position statement of the Working Group on Cardiovascular Thrombosis of the Spanish Society of Cardiology. *Rev Esp Cardiol* 2020; 73: 749-757. doi: <https://doi.org/10.1016/j.recresp.2020.04.006>.
 56. Agencja Oceny Technologii Medycznych i Taryfikacji. Polskie zalecenia diagnostyczno-terapeutyczne oraz organizacyjne w zakresie opieki nad osobami zakażonymi lub narażonymi na zakażenie SARS-CoV-2. 25.04.2020. Available at: https://www.aotm.gov.pl/media/2020/07/2020.04.25_zalaczenia-covid19_v1.11.pdf (Accessed: 22.02.2021).
 57. 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: 559. doi: <https://doi.org/10.1186/s13054-020-03273-y>.
 58. Longhitano Y, Racca F, Zanza C, et al. Venous thrombo-embolism in hospitalized SARS-CoV-2 patients treated with three different anticoagulation protocols: prospective observational study. *Biology (Basel)* 2020; 9: 310. doi: <https://doi.org/10.3390/biology9100310>.
 59. National Institutes of Health. Antithrombotic therapy – COVID-19 treatment guidelines. NIH, 2020. Available at: <https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy> (Accessed: 22.02.2021).
 60. Boston University School of Medicine. COVID-19 treatment algorithms. BMC 2020. <https://www.bumc.bu.edu/id/covid-19-response/covid-19-treatment-algorithms/> (accessed February 22, 2021).
 61. Kowalska J, Podlasiński R, Paciorek M, Pulik P. Strategia walki z pandemią COVID-19. Available at: <https://www.gov.pl/web/zdrowie/strategia-walki-z-pandemia-covid19> (Accessed: 05.12.2020).
 62. McBane RD, Torres Roldan VD, Niven AS, et al. Anticoagulation in COVID-19: a systematic review, meta-analysis, and rapid guidance from Mayo Clinic. *Mayo Clin Proc* 2020; 95: 2467-2486. doi: <https://doi.org/10.1016/j.mayocp.2020.08.030>.
 63. Susen S, Susen S, Tacquard CA, et al. Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring. *Crit Care* 2020; 24: 364. doi: <https://doi.org/10.1186/s13054-020-03000-7>.
 64. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. *J Thromb Thrombolysis* 2020; 50: 287-291. doi: <https://doi.org/10.1007/s11239-020-02145-0>.
 65. Vlot EA, Van den Dool EJ, Hackeng CM, Sohne M, Noordzij PG, Van Dongen EPA. Anti Xa activity after high dose LMWH thrombosis prophylaxis in covid 19 patients at the intensive care unit. *Thromb Res* 2020; 196: 1-3. doi: <https://doi.org/10.1016/j.thromres.2020.07.035>.
 66. Adie SK, Farina N. Impact of COVID-19 on monitoring of therapeutic unfractionated heparin. *J Thromb Thrombolysis* 2020. doi: <https://doi.org/10.1007/s11239-020-02250-0> [Epub ahead of print].
 67. Dutt T, Simcox D, Downey C, et al. Thromboprophylaxis in COVID-19: Anti-FXa – the missing factor? *Am J Respir Crit Care Med* 2020; 202: 455-457. doi: <https://doi.org/10.1164/rccm.202005-1654LE>.
 68. Wei MY, Ward SM. The anti-factor Xa range for low molecular weight heparin thromboprophylaxis. *Hematol Rep* 2015; 7: 80-83. doi: <https://doi.org/10.4081/hr.2015.5844>.
 69. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. *Anesth Analg* 2021; 132: 930-941. doi: <https://doi.org/10.1213/ANE.0000000000005292>.