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THROMBOPROPHYLAXIS IN COVID-19

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Abstract

The SARS-CoV-2 pandemic and its specific respiratory pathology has generated extensive research that has highlighted the specific nature of the disease (COVID-19). Thrombotic processes in the macrocirculation and microcirculation were among the first reported, accompanying respiratory (pulmonary) manifestations. Of the COVID-19 complications, thrombosis in the venous system (venous thrombosis and pulmonary embolism) and the atrial system (stroke) are the most numerous and severe in terms of evolution and prognosis. The prophylaxis of thrombotic processes in COVID-19, initially empirical, has gained a scientific basis based on research and experience of clinicians.

The current paper presents general data on macro- and microcirculatory thrombosis and the rationale for thromboprophylaxis. Thromboprophylaxis in non-hospitalized COVID-19 patients, "non-critical" and "critical" hospitalized patients and possible post-hospital thromboprophylaxis are presented.

Heparins (HGMM and HNF) are the most commonly indicated and used antithrombotic agents. Other antithrombotic agents - antiplatelets and direct anticoagulants (oral - DOAC) have a very limited and possibly negative role in thromboprophylaxis in COVID-19.

Keywords*: SARS-COV-2 pandemic, COVID-19, thrombosis, stroke, thromboprophylaxis.*

Abstract

Pandemia SARS-CoV-2 și patologia respiratorie pe care o determină au generat cercetări ample care au evidențiat natura specifică a bolii (COVID-19). Procesele trombotice în macrocirculație și microcirculație au fost printre primele raportate ca însoțind manifestările respiratorii. Dintre complicațiile COVID-19, tromboza în sistemul venos (tromboza venoasă și embolismul pulmonar) și sistemul atrial (accident vascular cerebral) sunt cele mai numeroase și severe din punct de vedere al evoluției și al prognosticului. Profilaxia proceselor trombotice în COVID-19, inițial empirică, a căpătat o bază științifică bazată pe cercetarea și experiența clinicienilor.

Lucrarea actuală prezintă date generale despre tromboza în macro și microcirculație și justificarea tromboprofilaxiei. Sunt prezentate tromboprofilaxia la pacienții nespitalizați cu COVID-19, pacienții internați „noncritici” și „critici” și posibila tromboprofilaxie post-spitalizare.



Internal Medicine

General Reviews

Heparinele (HGMM și HNF) sunt agenții antitrombotici cel mai frecvent indicați și utilizați. Alți agenți antitrombotici - antiplachetare și anticoagulante directe (orale - AOD) au un rol foarte limitat și posibil negativ în tromboprofilaxia în COVID-19.

Cuvinte cheie: *pandemie SARS-COV-2, COVID-19, tromboză, accident vascular cerebral, tromboprofilaxie.*

Thromboprophylaxis in COVID-19 - current data

Main thrombotic processes in COVID-19

Observational data and clinical investigations in patients with COVID-19 in the first waves of the pandemic have reported thrombotic or thromboembolic manifestations in the macrocirculation and microcirculation. Initial observations focused on the risk of venous thromboembolism (VTE) and later on thromboembolism in the arterial sector.

Published data in 2020 and 2021 on thrombotic events in COVID-19, are varied - in relation to the patient groups studied, the pandemic period and the type of thrombo-prophylaxis used. Most of the data come from 'non-critical' or 'critical' inpatient groups, with thrombotic events being rare and difficult to track in outpatients. Knowledge of thrombotic processes in COVID-19 and their extent, led to studies of thrombotic event prophylaxis and with the type of thromboprophylaxis used.

Among the most frequently reported and studied thrombotic events associated with COVID-19 are VTE and ischemic and hemorrhagic stroke. The VTE frequency in COVID-19 initially reported was 20-43%, relative to various stages of the pandemic (on average 26%)[1]. A meta-analysis of 48 studies with 18094 patients showed an overall incidence of VTE of 17%, 12% for DVT (deep vein thrombosis) and 7% for pulmonary embolism (PE). The incidence of VTE was higher in ICU (45%), in severely ventilated, mechanically ventilated, hypoxaemic patients with numerous thrombogenic risk factors[2]. In contrast to figures reported in a study of 2505 COVID-19 patients without ICU hospitalization, the incidence of PE was 2.2%, similar to DVT[3].

Pulmonary embolism (PE) associated with COVID-19 is a particular problem in the VTE set due, among other things, to the difficulties in diagnostic (imaging) accuracy and the potentially severe course. In retrospective studies, PEs in severe COVID-19 had an incidence between 8.3% and 23% compared with 0.1% in the general population[2]. In a

rigorous French study of 1240 severe patients, PE was demonstrated in 8.3% of cases (angio CT confirmation). Approximately 25% of patients had mechanical ventilation[4].

Global data on the incidence of thrombo-embolic complications in COVID-19 patients admitted to ICU are provided by a Dutch study. The cumulative incidence for PE, DVT, ischemic stroke and acute myocardial infarction was 31%. Confirmed VTE (by CT angio and/or venous Doppler) was 27% for PE 8.3% and 3.7% for arterial thrombosis. Thromboembolic events developed in patients with standard thromboprophylaxis (interesting!)[5].

Mortopathological studies have demonstrated the presence of obstructive thrombosis on large pulmonary vessels and frequently on the microcirculation (together with inflammatory elements).

Ischaemic and haemorrhagic stroke is the most severe neurological complication in COVID-19; its incidence of all neurological events is estimated to be about 2.5%. Although stroke associated with COVID-19 is a less common occurrence than VTE, it is a severe complication with a mortality of approx. 20%[6,7].

The incidence of stroke in patients with COVID-19 was initially estimated at 5.0%[6]. Subsequently published studies, review-ri and meta-analyses, have provided different data and lower figures. A meta-analysis with 108371 patients with COVID-19 and 1200 with Stroke, reported the incidence of acute Stroke in 1.4% of patients[7]. In other meta-analyses or reviews - respectively with 55176 and 27676 patients, an incidence of 1.74% and 1.3% is mentioned[6,8].

Regional differences are also mentioned; in the Asian region the incidence reaches 2.7%. In severe forms of COVID-19, mainly cared for in the ICU, the incidence of acute stroke is higher - respectively 3.3% versus 0.6% in non-critical patients[7]. Acute stroke develops between 7-10 days after the first signs of COVID-19, during which time the prothrombotic state is established in the conditions of the inflammatory syndrome. Acute stroke associated with COVID-19 is predominantly ischemic (82.8%) compared to hemorrhagic stroke (17.2%). Correct diagnosis of stroke type is of prognostic importance (more severe in HS) and of therapeutic attitude. Patients with stroke associated with COVID-19, compared to stroke without COVID-19, have significant clinical, morphological, developmental and end-of-treatment peculiarities[8, 9]. Patients are older and in addition have more comorbidities (hypertension, DZ, chronic kidney disease, coronary artery disease), predisposing factors for the development of stroke.

- The Stroke is more severe, clinically assessed by NIHSS score (moderately severe)
- On MRI and CT angiography, occlusion of large cerebral vessels (more common) and multiple ischemic lesions are found[10].
- In evolution, Stroke is more severe either due to complications related to the Stroke itself or COVID-19: acute respiratory distress, cerebral edema or hemorrhagic transformation, development of acute MI. Stroke severity may be due to multi-organ damage (AKI, acute liver injury)[10].
- Inflammation markers have high values (especially D-dimer, CRP) signalling the acute process of thromboinflammation.
- Finally, mortality in acute stroke is high - even with current thrombolytic or interventional treatment and ranges from 31% to 19.4%[5,8]. The prognosis of the acute stroke patient is determined



primarily by the type and severity of stroke and less by COVID-19.

Thrombotic processes are not limited to the macrocirculation in COVID-19 and are also present in the microvasculature. Platelet-rich thrombi have been identified in the pulmonary, renal, hepatic, cardiac microvasculature[1]. In COVID-19 the lung injury extends beyond the alveolar structure to the pulmonary capillary level with microthrombus formation. The cytokine inflammatory process causes a prothrombogenic status.

Patients with COVID-19 may develop acute kidney injury (AKI) over time, especially in severe cases. Microscopic studies have identified aspects of microangiopathy, with fibrin thrombi in the glomeruli, micro-thrombosis in the glomerular capillaries and acute tubular necrosis[11]. COVID-19 is also associated with acute liver injury. Mechanisms of injury are systemic inflammation, sinusoidal microthrombosis, hepatic ischaemia and drug toxicity. Microthrombosis was identified at the necropsy as well as at the liver biopsy.

Pathophysiological mechanisms in COVID-19

The underlying pathophysiological processes in COVID-19 are inflammation and thrombosis-coagulopathy. Endothelial injury by SARS-CoV2 is the pathological process linking inflammation to thrombosis. Research in recent years has confirmed the hypothesis that COVID-19 is a disease of the vascular endothelium or endothelium[11].

The vascular endothelium is the interface between vascular blood flow and adjacent tissue. It has numerous functions that contribute to homeostasis (vasomotricity, inflammation, oxidative stress, vascular permeability). These protective functions/ mechanisms contribute to COVID-19 disease when endothelial defence functions are overwhelmed.

Infection with SARS-CoV2 initially leads to spike protein attachment of AGE-2 receptors from pneumocytes, but also from various organs or tissues that have AGE-2 receptors. Viral replication and endothelial activation are followed by the release of protoinflammatory agents via exocytosis. Exocytosis is a secretory response to injury whereby endothelial granules fuse into the endothelial membrane and are released into the bloodstream.

Endothelial granules contain vWF, Prelectin and other inflammatory cytokines IL-1, IL-6, 1B (interleukins) and TNFx. von Willebrand factor (vWF) mediates platelet adhesion and aggregation. Activated endothelium expresses adhesion molecules (e.g. Prelectin) that attract leukocytes, macrophages, cytokines that migrate into the subendothelial space and affect the basement membrane.

Agent	Profilactic	Therapeutic
HNF	5000 U x 2/day	Intravenous, adjusted by APTT
HGMM	Enoxaparin 40 mg/ once daily Dalteparin 5000 IU/ once daily	Enoxaparin 1 mg/ kg x 2 times/day Dalteparin 200 IU/kg once daily
DOAC	Rivaroxaban 10 mg/day Apixaban 2.5 mg x 2/day	Rivaroxaban 20 mg/ once daily Apixaban 5 mg x 2/day

Table 1. *(after 16 amended)*

Inflammatory cells stimulate tissue factor (TF) expression at the endothelial surface and as a result activate the coagulation cascade and develop microthrombosis[12,13].

The development of microthrombosis, and then vascular macrothrombosis, are a direct result of endothelial injury, TF activation and the increase of procoagulant factors such as F VIII and vWF. TF and F VII activate the extrinsic coagulation pathway, thrombin formation and localized intravascular coagulation or coagulopathy in severe forms of COVID-19[14,15].

COVID-19-associated coagulopathy is characterized by thrombocytopenia moderation, increased D-dimer, increased fibrin degradation products and vWF[15].

In summary, thrombosis processes in the vascular system are the result of endothelial injury and procoagulant and proinflammatory conditions. Endothelial injury and endothelial activation also initiate vascular inflammatory (microvascular) processes, which release cytokines, which in turn can trigger endothelial erythrocytosis. The inflammatory response and excessive cytokine elevation manifests as cytokine storm with systemic damage, including vascular microthrombosis (pulmonary, renal, hepatic, coronary microcirculation)[12]. In COVID-19 the association of inflammation, thrombosis-coagulopathy, legitimizes the concept of thromboinflammation or immunothrombosis[14].

Thromboprophylaxis in COVID-19: means, indications and recommendations

Knowledge of the pathophysiological elements of macro- and microcirculatory thrombotic processes in COVID-19, the data of potential severity of disease progression, made extensive thromboprophylaxis studies necessary.

Determining the opportunity of thromboprophylaxis in COVID-19 infection led to several key questions: what type of antithrombotic is needed? What doses are necessary and effective? Duration of treatment? The answers to these questions have been provided by the results of



observations and clinical trials and have been reported in hundreds of scientific articles, reviews and meta-analyses. Doses, efficacy and adverse effects for antiplatelet agents, anticoagulants, including direct anticoagulants (DOACs) have been studied.

The main types of antithrombotic medication and doses used in the studies (and currently) are given in Table I. (In some studies "intermediate doses" between prophylaxis and treatment have been used, e.g. UFH 7500 IU x 2/ once daily; Enoxaparin 40 mg x 2/day or 80 mg/ once daily). The decision to use antithrombotic medication in prophylactic doses, but especially in therapeutic doses, requires an assessment of the thrombotic or haemorrhagic risk in each individual case.

The review of studies reporting results of the use of antithrombotic agents in COVID-19 patients allowed the development of Practice Guidelines. National and international scientific organisations have published Practice Guidelines on the type and doses of antithrombotic agents to be used (which should be administered) at all stages of care of COVID-19 patients.

Among the most important guidelines published in the last 2 years are the "European Respiratory Society", "National Institute of Health (USA)", "International Society of Haemostasis and Thrombosis". Thrombo-prophylaxis guidelines are largely similar, with some differences resulting from the stages of the pandemic, types of antivirals used, batch characteristics, etc.

Conventionally, thromboprophylaxis guidelines are formulated differently for COVID-19 outpatients, for "non-critical" or "critical" hospitalised patients and for post-hospital treatment.

Recently (2022) an ISTH Guideline for antithrombotic treatment in COVID-19 was published by experts based on published research and studies including in 2021[15]. The guideline contains 12 recommendations for specific situations in which patients with COVID-19 infection find themselves. According to the ISTH Guidelines (2022) the recommendation classes are 1 (strong), 2a (moderate), 2b (weak) and 3 (no benefit or "harm"). The level of evidence for each recommendation is graded A, B, C. The ISHT guidelines being the most recent - with updated data, are considered basic for medical practice, and specifically mentioned in the current reference[16].

Patients with SARS-CoV-2 infection who are followed up and treated on an outpatient_(non-hospitalized) basis are generally patients with a milder form of the disease in whom major thrombotic events very rarely develop. Initially therapy focused on the use of antiplatelet versus anticoagulant therapy. Cohort studies using aspirin vs placebo showed no benefit on mortality and

symptomatic thrombosis; instead a (small) increase in minor or clinically relevant bleeding has been reported[17]. Aspirin evaluation and efficacy have also been reported in the RECOVERY trial in patients hospitalized with COVID-19. Aspirin was not associated with reduced 28-day mortality or disease progression; bleeding risk was reconfirmed (RECOVERY)[18]. The use of DOACs, namely apixaban 2.5 mg x 2/day and 5 mg x 2/day, in thromboprophylaxis has shown no benefit in preventing thrombotic events and its sequelae[17,19].

The ISTH Guidelines summarize thrombo-prophylaxis recommendations for patients with COVID-19 followed and treated on an outpatient (non-hospitalized) basis.

- In most non-hospitalized, symptomatic-stable COVID-19 patients, antithrombotic treatment is not necessary. In selected cases at high thromboembolic risk (history of VTE, bed rest, obesity, non-hospitalized congestive heart failure), prophylactic-dose DMH or UFH may be used.
- In non-hospitalized patients with symptomatic COVID-19 infection, initiation of antiplatelet therapy is not effective in reducing the risk of hospitalization, arterial and venous thrombosis, or mortality (no obvious level B benefit). Similar provisions are provided for thromboprophylaxis with DOAC.

Patients hospitalized for COVID-19, have varied forms of the disease and thrombotic complications are more common, especially in patients hospitalized in ICU. For "non-critical" and "critical" patients the results of thromboprophylaxis were different and the results are currently different.

Antithrombotic therapy for non-critical patients with COVID-19

This type of patient represents the largest proportion of COVID-19 patients hospitalised. Several observational studies in hospitalized noncritical patients have observed reduced mortality risk using low-dose MGMT or UFH compared to no prophylaxis[9,17,20]. Prophylactic doses of heparins would reduce mortality by 24%-82% or progression to thromboembolism by 14%[6, 7]. Such results have led to the recommendation that all patients hospitalized with confirmed or suspected COVID-19 should be treated with heparins for prophylaxis of thrombotic events - due to the inflammatory state[16,20].

Currently, there are multiple recommendations for antithrombotic therapy for non-critical, hospitalized patients:

- For non-critical patients, prophylactic dosing of MMPH or UFH is recommended over no prophylaxis to reduce the risk of thromboembolism or possible death (1 level evid B).
- For selected non-critical patients (especially based on high D-dimer values or who accumulate multiple thromboembolic risk factors) therapeutic dosing of MMPH or UFH is beneficial and preferred to prophylactic or "intermediate" dosing of heparins (1 level evid A) to reduce the risk of thromboembolism and organ failure[21,22].
- Intermediate doses of heparins in the prophylaxis of thrombotic events in COVID-19 have been used in several observational studies with unclear results[23, 24]. Thus, in the ISTH Guidelines, intermediate doses are not recommended in selected non-critical patients, retaining prophylactic



heparin dose recommendations.

- The term "selected patients" includes patients with high D-dimer values or who accumulate multiple thrombo-embolic risk factors (e.g. infection, prolonged immobilization, etc.). The ISTH guidelines have two additional provisions for therapy in non-critical hospitalized patients[16].
- The addition of antiplatelet agents to prophylactic treatment is potentially harmful and should not be used ("harm" level evid A).
- The use of therapeutic doses of DOAC is of no benefit in reducing the risk of thromboembolism ('no benefit' level B evidence).

The additional claims reported are based on clinical studies. Thus the RECOVERY trial (14892 patients) reported a lack of benefit of antiplatelet therapy added to heparin thromboprophylaxis[18]. Similar findings were reported in a study using clopidogrel (P2Y12 inhibitor)[25].

The use of DOAC in therapeutic doses in thromboprophylaxis has led to rather negative results. The ACTION study compared the efficacy and safety of rivaroxaban in therapeutic doses or standard heparin prophylaxis in patients with COVID-19 and high D-dimer levels. Therapeutic doses of rivaroxaban or enoxaparin followed by rivaroxaban for 30 days did not improve clinical outcome (DVT, PE, Stroke) but increased bleeding rate (8% vs 2% p = 0.01). The study concludes that the use of therapeutic doses of rivaroxaban or other DOACs in COVID-19 does not benefit and should not be prescribed[26].

The approach to antithrombotic therapy in COVID-19 patients hospitalized with critical illness is partially different from that used in non-critical patients. Critical patients are defined by clinical conditions requiring ICU admission (e.g. haemodynamic support, respiratory support, acute kidney injury).

The important issue to be defined concerns the appropriateness of using prophylactic or therapeutic doses of MMPH/FNH or other types of anticoagulants.

Patients with severe disease are admitted to the ICU, where they have differentiated therapy (mechanical ventilation) and prolonged hospitalisation. The risk factors for thrombotic events in the venous or arterial sector are increased so that in practice there is a tendency to escalate antithrombotic doses from prophylactic to therapeutic doses.

Multiple clinical trials have attempted to answer this question and the results are questionable[24, 27]. Thus, a platform study (n = 1098) in critically ill patients was prematurely terminated without demonstrating a difference in patient outcome between

prophylactic and therapeutic doses of HGMM/ HNF[28]. A smaller study showed no significant difference for patient outcome between prophylactic and therapeutic doses of heparins[24].

The ACTION study looked at the efficacy and safety of anticoagulant treatment (full) versus prophylactic dosing in 3331 patients hospitalized with COVID-19 and D-dimer augmentation.

It concluded that anticoagulation therapy with rivaroxaban versus prophylactic dosing did not improve clinical outcome but increased bleeding[26].

A recent meta-analysis pooling data from 5 randomized trials reported results with anicoagulants (full) versus prophylactic doses. Two studies of 635 patients with moderate COVID-19 showed that therapeutic doses may decrease the risk of thrombotic events and death compared with standard prophylactic doses. In 3 other clinical trials with 2226 patients, anticoagulation (full) in critically ill patients was associated with increased (moderate) overall mortality of major bleeding and acute organ failure.

Expert opinion on the appropriateness of anticoagulant (full) treatment in critically ill patients is divided. The European Respiratory Society recommends full anticoagulation in critically ill patients with COVID-19, whereas the ISHT guidelines have different recommendations. The American Society of Haematology suggests prophylactic dosing for critical patients with COVID-19 who are not suspected of VTE.

The recently published ISTH guidelines provide three relatively simple recommendations:

- In critically ill patients hospitalized for COVID-19, the intermediate dose of HGMM/ HNF is not recommended, as opposed to prophylactic dosing, to reduce the risk of adverse events, including mortality and thrombo-embolism (no obvious level B benefit).
- In critically ill patients hospitalized for COVID-19, the therapeutic dose of MMPH/FNH is not recommended, as opposed to the prophylactic dose of MMPH/FNH (no benefit level B evidence).
- In "selected" critical patients, the addition of an antiplatelet agent to the prophylactic dose of HGMM/ HNF, is not well established and may be considered for mortality reduction (2b level evid B).

In conclusion, for critically ill patients hospitalized for COVID-19, recommendations are cautious: prophylactic doses of DMH/FH are preferable to therapeutic doses; therapeutic doses of heparins do not improve disease progression and are most likely harmful[15,27].

A proportion of patients with COVID-19 at **hospital discharge** still have markers of hypercoagulability, e.g. elevated CRP and D-dimer values, conditions that maintain the risk of thromboembolism. Such situations raise the question of extending antithrombotic treatment for a period of time post-hospital. Typically in patients not selected with COVID-19, the risk of post-hospital VTE is low, but coupled with the risk of bleeding raises questions about the appropriateness of extending prophylaxis[31]. In the ACTION study rivaroxaban in therapeutic dose for a 30-day period (hospital and post-hospital) was not superior to prophylactic heparin dose and was associated with higher risk of bleeding[26].

Possible extension of post-hospital thromboprophylaxis requires an oral anticoagulant; heparin thromboprophylaxis appears difficult for the patient. Rivaroxaban



in a low dose (10 mg/day) as effective post-hospital thromboprophylaxis was used in the MICHELEE study[32].

The study compared a group of patients receiving rivaroxaban 10 mg/day for up to 35 days with a group without anticoagulant treatment. Symptomatic, asymptomatic or fatal VTE, arterial thromboembolism and death at 35 days were followed. Thromboprophylaxis efficacy with rivaroxaban was 3.0% compared with 9.0% for the no anticoagulation group, no major bleeding was reported. The results of the rivaroxaban trials were confirmed by a registry of early discharged post-COVID-19 patients[31].

Based on existing data the ISTH Guidelines (2022) state that in selected patients who have been hospitalized for COVID-19, treatment with 30-day prophylactic dose rivaroxaban can be considered for VTE risk reduction (2b level evid B).

Thrombotic events resulting in macro-circulation, especially VTE and Stroke, and microcirculation, are the most severe complications in COVID-19, after acute respiratory distress. They develop relatively early in COVID-19, with severe progression, through a specific pathophysiological mechanism: thromboinflammation or immunothrombosis.

The primary element leading to thrombosis is SARS-CoV2 aggression at the epithelial (lung) level, followed by endotheliitis and inflammation, thrombosis and coagulopathy.

Thromboprophylaxis, using heparins (HGMM or HNF) in prophylactic doses, has proven effective and safe in the majority of hospitalized patients and in special conditions and outpatients. For "critical" patients cared for in the ICU, the use of prophylactic doses or therapeutic doses, is a topic under discussion, with different approach in the current Guidelines. Direct anticoagulants (DOACs) do not have a defined role in thromboprophylaxis in COVID-19.

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