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IM-POINT OF VIEW

Switch from oral anticoagulants to parenteral heparin in SARS-CoV-2 hospitalized patients

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Abstract
The development of COVID-19 syndrome in anticoagulated patients, and especially their admission to intensive-care units with acute severe respiratory syndrome (SARS-CoV-2), expose them to specific problems related to their therapy, in addition to those associated with the acute viral infection. Patients on VKA hospitalized with SARS-CoV-2 show high instability of PT INR due to the variability of vitamin K metabolism, diet, fasting, co-medications, liver impairment, and heart failure. Patients on DOAC are exposed to under/over treatment caused by significant pharmacological interferences. In consideration of the pharmacological characteristics of oral anticoagulant drugs, the multiple pharmacological interactions due to the treatment of acute disease and the possible necessity of mechanical ventilation with hospitalization in intensive-care units, we suggest replacing oral anticoagulant therapies (VKA and DOAC) with parenteral heparin to avoid the risk of over/under treatment.

Keywords SARS-CoV-2 · COVID-19 · VKA · DOAC · LMWH

The novel coronavirus infection COVID-19 pandemic has spread all over the world, as declared by World Health Organization on March 11th 2020 [1, 2].

Italy, particularly the northern regions, has been notified as the first European country in which severe acute respiratory syndrome due to SARS-CoV-2 has spread, involving thousands of people many of whom are now hospitalized [2].

Due to the high prevalence of oral anticoagulant drugs in the western countries, which in this area reaches 2.2% of the total population, an increasing number of patients treated with vitamin K antagonists (VKA: warfarin or acenocoumarol) or direct oral anticoagulants (DOAC: dabigatran, apixaban, rivaroxaban, and edoxaban) are hospitalized with COVID-19.

DOAC represent the treatment of choice for many clinical indications, such as the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and the prevention and treatment of venous thromboembolism (VTE), and VKA antagonists remain the only available drugs to prevent valve thrombosis and thromboembolic events in patients with prosthetic heart valves and in those in whom DOAC are contraindicated [3–7].

The development of COVID-19 infection in anticoagulated patients, and especially their admission to intensive-care units with acute severe respiratory syndrome (SARS-CoV-2), expose them to specific problems related to their therapy, in addition to those associated with the acute viral infection.

In particular, patients on AVK show a high instability of PT INR, specifically due to the variability of vitamin K metabolism, diet, fasting, co-medications, liver impairment, and heart failure, which make physicians dealing with difficulties in strictly maintaining the therapeutic range [3, 5, 7].

On the other hand, DOAC are currently administered at fixed dose without routine laboratory control [3], even if a high inter-individual variability has been shown [8].

Recently, some studies underlined the usefulness of DOAC measurement in addressing specific treatment approaches, such as on the occasion of bleeding or thromboembolic complications, surgery, or invasive maneuvers, thrombolytic therapy in patients with acute stroke, to highlight drug–drug interactions [9].

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Table 1 Heparin replacement in patients on oral anticoagulant therapy (AVK and DOAC) with VTE, NVAF or prosthesis heart valves, hospitalized with SARS-CoV-2

Drugs	VTE	NVAF	Mechanical or recent biological heart valves
VKA	Stop VKA; when PT INR < 2.0: -LMWH or UH if CrCl<15mL/min, at therapeutic dose	Stop VKA; when PT INR < 2.0: -LMWH or UH if CrCl<15mL/min, at therapeutic dose	Do not stop VKA and maintain therapeutic range through daily control of INR If impossible to continue VKA, LMWH 100UI/kg bid or UH, with a strict control of anti-FXa, maintaining the upper limit of therapeutic range
DOAC	Stop DOAC; after 12–24 h depending on mono- or bi- administration: -LMWH or UH if CrCl<15mL/min, at therapeutic dose	Stop DOAC; after 12–24 h depending on mono or bi-administration: -LMWH or UH if CrCl<15mL/min, at therapeutic dose	–

DOAC interact with P-glycoprotein and/or cytochrome P450 (CYP)-based metabolic pathways. Many classes of drugs cause drug–drug interactions, in such a way modifying the DOAC pharmacodynamic and pharmacokinetic profile and causing a remarkable decrease or increase of their anticoagulant action. On this basis, the use of DOAC is generally discouraged in association with several classes of drug such as antiviral drugs, rifampicin, fungostatics, and some antineoplastic agents [10, 11].

Patients hospitalized with COVID-19 respiratory syndrome are commonly treated with multiple drugs as antiviral therapies (lopinavir/ritonavir, darunavir), tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor), chloroquine or hydroxychloroquine, antibiotics (levofloxacin, ceftriaxone, azithromycin, and amoxicillin/clavulanic acid), steroids (methylprednisolone, dexamethasone), nonsteroidal anti-inflammatory drugs, bronchodilators, and immunosuppressive drugs.

Specifically antiviral therapies strongly interact with DOAC, exposing patients to significant increase of DOAC plasma levels [10].

The multiple drug–drug interactions (antiviral, antibiotics, antihypertensive, bronchodilators, and immunosuppressive drugs), in addition to metabolic alterations that are induced by the acute disease, can cause unpredictable and unstable DOAC anticoagulant effect, exposing patients to the risk of uncontrolled bleeding or thrombotic complications [10, 11].

Moreover, in patients with SARS-CoV-2, the coagulation function is significantly deranged compared with healthy people [12].

Owing to the fact that DOAC measurements are not commonly available in many hospitals yet, and that patient clinical conditions can rapidly deteriorate in a short time frame, special cautions should be adopted for managing DOAC patients during acute COVID-19 respiratory infection.

In consideration of the pharmacological characteristics of oral anticoagulant drugs, the multiple pharmacological interactions due to the treatment of acute disease, and the possible necessity of mechanical ventilation with hospitalization in intensive-care units, we suggest replacing oral anticoagulant therapies (VKA and DOAC) with parenteral low-molecular-weight heparin (LMWH) or unfractionated heparin (UH) to avoid the risk of over/under treatment.

Moreover, parenteral administration strongly facilitates the antithrombotic treatment in ventilated or intubated patients.

This indication should be adopted in all patients except for those with prosthetic heart valves, in whom VKA continue to remain the drugs of choice [5, 13]. In this group of patients, a strict monitoring of PT INR is required to maintain the therapeutic range, through a daily laboratory control of PT INR. In case of impossibility to maintain VKA antagonists, LMWH 100UI/kg bid or UH, maintaining a strict control of anti FXa at the upper limit of therapeutic range, can be considered a practical option [14–16].

Strategies proposed, summarized in Table 1, are practical indications that could guide physicians on OAT patient management hospitalized with SARS-CoV-2.

While waiting for evidences from proper clinical trials, patients should be treated with anticoagulants, at therapeutic regimen, especially because their critical condition increases thrombotic risk [17].

In the meantime, and for pragmatic reasons, we recommend the adoption of the therapeutic protocol that is described in Table 1, where OAT is replaced by LMWH or UH, with the addition of the following specifications:

1. Specific DOAC plasma measurements should be considered before starting heparin in patients with impairment of renal function, potential pharmacological interferences, or other critical conditions, considering the possible drug accumulation.
2. We suggest heparin anti-factor Xa measurement (aFXa) in patients with severe respiratory distress associated with impairment of renal or hepatic function. For

LMWH levels determined 4 h after the last LMWH administration: therapeutic range = 0.5–1.2 UI/ml. For UH: aFXa = 0.3–0.7 UI/mL; aPTT ratio = 1.5–2.5.

3. Periodical platelet count and measure of creatinine clearance are indicated during heparin treatment.

These indications are the result of expert opinion in this dramatic health emergency when decisions have to be rapidly taken and evidences derived from rigorous clinical trials are lacking.

Compliance with ethical standards

Conflict of interest Authors received no specific foundings for this work and declare no conflict of interest.

Ethical standard All procedures performed in study involving human participants were in accordance with the ethical standard of the institutional research committee and with the 1964 Helsinki declaration and is its later amendments or comparable ethical standards.

Research involving human participants or animals This article does not contain any study with animals performed by any of the authors.

Informed consent No informed consent is required.

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