Update on the management of vascular patients with COVID-19

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Abstract Attention has to be payed to patients with vascular disease (VD) cardiovascular risk factors (VD-CVR) and COVID-19.
In fact, COVID-19 is also manifested with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and venous thromboembolism (VTE) or arterial thrombosis and VP are a frail population. Predisposing risk factors to severe COVID-19 are male sex, underlying cardiovascular disease, or cardiovascular risk factors including non-controlled diabetes mellitus or arterial hypertension, obesity, and advanced age. The VAS-European Independent Foundation in Angiology/Vascular Medicine has recently published an integral strategy for the management of patients with VD or cardiovascular risk factors (VD-CVR) and COVID-19.
This paper represents a short summary.

Keywords COVID-19, vascular disease, cardiovascular risk factors, peripheral arterial thrombosis, deep vein thrombosis

In Europe, the second wave of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic starts to ravage people's health and the continuously increasing number of patients with Coronavirus Disease 2019 (COVID-19) destabilizes health care systems. Governments are strengthening "barrier measures" and calling for the individual responsibility of citizens, while localized or even national lockdowns - the ultimate options to control SARS-CoV-2 spread - are being applied. So we are witnessing, seven months later, the same phenomenon which led to the generalized confinement which has social, psychological and financial cost. COVID-19 is a systemic, potentially severe and life-threatening disease, triggered by the SARS-CoV-2 infection involving both immune and inflammatory responses, endothelial cell dysfunction, complement activation and hypercoagulable state.

In March 2020 the *World Health Organization (WHO) officially declared the SARS-CoV-2 infection as a pandemic and classified COVID-19 in three levels of severity*: (i) *Critical illness* defined in patients with acute respiratory distress syndrome or sepsis with acute organ dysfunction; (ii) *Severe illness* designated when the patients have fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress, or pulse oximeter oxygen saturation ≤93% on room air; (iii) *Non-severe type* in patients without any of the above conditions.

COMPASS-COVID-19 RAM		
Predictors for risk of worsening disease		**Score**
Obesity (BMI>30)		19
Male gender		10
Compensated DIC-ISTH score ≥5		9
Thrombopenia (Platelet count < 100.000/μL) :	1	
Prothrombin Time prolongation (> control+ 3 sec):	1	
D-Dimers increase (>500 for age <60 years; >600 ng/ml for age 60 - 69 years; >700 ng/ml for age 70 - 79 years; >800 ng/ml for age 80 - 89 years; >900 ng/ml for age 90 - 99)	1	
Antithrombin decrease (<lower normal limit established by the laboratory)	1	
Protein C decrease (<lower normal limit established by the laboratory)	1	
Total	≥5	
Lymphocytes $<10^9$/L		8
Hemoglobin <11 g/dL		8
Total		**≥ 18 : high risk** **< 18 : low risk**

Table I *- The COMPASS-COVID-19 score for the evaluation of the risk for worsening disease in patients with COVID-19.*

While most people with COVID-19 develop only non-severe illness, usually characterized by fever, cough, myalgias and breath shortness, approximately 15% develop severe disease that requires hospitalization and oxygen support and 5% present critical illness requiring admission to an intensive care unit (ICU). The mortality rate in patients with critical illness raised up to 50% at the beginning of the epidemic and progressively dropped to about 35% to 45% indicating a substantial improvement of the therapeutic protocols.

Microvascular thrombosis at the lungs and other organs as well as pulmonary embolism (PE) are major causes of morbidity and mortality in patients with COVID-19. Hypercoagulability is a frequent hematological alteration in hospitalized patients with COVID-19 and predictor of disease worsening. Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is more frequent in hospitalized patients with COVID-19 as compared to patients hospitalized for other acute medical illness even when recommended pharmacological thromboprophylaxis is administered.

Epidemiological data initially published from China and later from other countries showed that patients with COVID-19 and vascular disease or cardiovascular risk factors[i] (obesity, diabetes, hypertension) are at high risk for disease worsening. Ischemic stroke, carotid artery disease, coronary artery disease, peripheral artery disease involve endothelial cell dysfunction and have an age-standardized prevalence from 5000 to 9000 cases per 100000 persons varying by country. The prevalence of cardiovascular risk factors (i.e. obesity, diabetes mellitus or arterial hypertension) is even higher. Consequently, following SARS-CoV-19 infection, patients with COVID-19 and vascular disease or cardiovascular risk factors (VD-CVR) are at risk for severe COVID-19 and critical illness.

The VAS-European Independent Foundation in Angiology/Vascular Medicine, facing the magnitude and the duration of the SARS-CoV-2 epidemic and the absence of a specific vaccine, responded to the urgent need for an integral and targeted strategy aiming the prevention of SARS-CoV-2 infection in vascular patients and the management of the COVID-19 vascular complications (in

patients with symptomatic disease) which may lead to disease worsening[1].

To this aim, antithrombotic treatment with low molecular weight heparins (LMWH) and some of the direct orally active anticoagulants (DOAC), is a cornerstone therapy for patients with COVID-19 and VD-CVR. Antithrombotic therapy targets both the downregulation of the hypercoagulability related disease worsening and the prevention of VTE[2-7].

Based on a comprehensive analysis of the literature and the recommendations published by the ISTH, the American Society of Hematology (ASH), the Thrombosis Collaborative group and the Chest, VAS proposes an integral strategy for the management of patients with VD-CVR which aims (a) the prevention of SARS-CoV-2 infection and (b) the management of vascular disease and cardiovascular risk factors and diagnosis of peripheral artery disease (a common but underdiagnosed vascular disease) (c) the prompt identification of the patients with COVID-19 who are at high risk of disease worsening or VTE. The recommendations of VAS for patients with VD-CVR are organized as follows

- **1. Management of COVID-19 at the level of primary health care system**: there is an urgent need to organize a medical network, using eHealth technologies, aiming the management of patients with VD-CVR during SARS-CoV-2 epidemic. Principal aims of this COVID-19 based Vascular Network are:
    - a. Systematic assessment for diagnosis of PAD particularly in citizens older than 65 years is of major importance at this level.
    - b. Identification of patients with VD-CVR at the community and registered at the regional COVID-19 centers and Angiology/ Vascular Medicine Centers when available.
    - c. Elaboration of educational programs for patients with VD-CVR and physicians, particularly general practitioners and family doctors, aiming their training on early recognition COVID-19, evaluation of the risk of COVID-19 worsening and the implementation of the recommendations for the diagnosis and treatment of COVID-19.
    - d. Close follow-up of patients with VD-CVR and non-severe COVID-19 who receive medical care at home. These patients should be prioritized for hospital admission in case of COVID-19 worsening.
    - e. Medical care and management of vascular complications in patients with VD-CVR and COVID-19 includes antithrombotic treatment. LMWH is the first line antithrombotic treatment in patients hospitalized with COVID-19 because they offer predictive and stable antithrombotic effect following subcutaneous injection and show less than unfractionated heparin (UFH) non-specific binding with plasma protein, particularly during the cytokine storm. In hospitalized patients with COVID-19, DOACs and vitamin K antagonists (VKA) should be replaced by LMWH due to potential interactions with antiviral or convalescence treatments. In case that DOACs treatment cannot be replaced by LMWH the interactions with the other drugs should be carefully controlled at the website http://www.covid19-druginteractions.org/. If these interactions exist monitoring of peak and trough levels of DOACs concentration in plasma is encouraged. DOAC should be preferred for antithrombotic treatment in patients with COVID-19 who receive medical care at home in order to avoid the purden of the daily subcutaneous injection of LMWH that could reduce patients' adherence to the treatment and also expose nursing stuff to contamination risk. Antiplatelet agents are corner-stone treatment for primary and secondary prevention of arterial thrombosis. Physicians who take care of patients with VD-CVR and COVID-19 should control adherence and compliance of the antiplatelet treatment according to the recommendations of the relevant consensus statements. Patients should continue to be treated with the recommended antihypertensive therapy and lipid lowering agents during their disease trajectory.

- **2. Evaluation of the risk for disease worsening and management of hypercoagulability, in patients with VD-CVR and COVID-19**. A RAM for disease worsening adapted for SARS-CoV-2 infection is an urgent need for prompt and targeted treatment of patients with COVID-19. Hypercoagulability is a frequent and early manifestation of coagulopathy in patients with COVID-19. Among the limited number of hypercoagulability biomarkers studied so far, increase of D-dimer is correlated with the COVID-19 severity risk for ICU admission and mortality. However, D-dimer cannot be used as a "stand-alone" test in the management of patients with COVID-19.

- a. The most updated COVID-19 panel of hypercoagulability tests in patients with COVID-19 (COAG-COVID-19 panel) includes: Hemoglobin, platelet count, lymphocyte count, PT, aPTT, Fibrinogen, D-dimer, Antithrombin activity and Protein C activity.
- b. The COMPASS-COVID-19 score (Table I) responds to the need for prompt evaluation of disease worsening , can be applied in hospitalized as well as out-patients with COVID-19 and is available on line at www.medupdate.eu. Patients should be routinely assessed, every one or two days from COVID-19 diagnosis, according to the clinical evolution and the judgment of the treating physician.
- c. Patients hospitalized or receiving medical care at home who are at high risk for disease worsening should receive antithrombotic treatment aiming the prevention of pulmonary intravascular coagulation, management of disseminated intravascular coagulation and prevention of VTE.
- d. Consumption coagulopathy is not a frequent alteration in patients with COVID-19. Disseminated intravascular coagulation (DIC) is a life-threatening syndrome which is an acquired syndrome characterized by the intravascular activation of coagulation and causes damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction. It is important to underline that according to the ISTH scientific subcommittee, DIC may present as (a) compensated activation of coagulation with subtle hemostatic dysfunction and increase in thrombotic risk without obvious clinical symptoms. This phase is characterized by an imbalance between activation and inhibition of the coagulation system. Deficiency of natural coagulation inhibitors (principally antithrombin and protein C) together with increase of D-dimer are early coagulation abnormalities in patients with compensated DIC. (b) overt DIC with significantly reduced hemostatic potential. This phase is characterized by the absence of normal regulatory mechanisms and collapse of hemostatic forces because of consumption of platelets, coagulation factors and fibrinogen. This condition is also known as “consumption coagulopathy.” Overt DIC is associated with both bleeding and thrombotic manifestations including both microvascular thrombosis and thrombosis of larger vessels. Compensated DIC may progress to overt DIC. Patients with COVID-19 do not present overt disseminated intravascular coagulation (DIC) unless hospitalization is complicated with sepsis. The compensated DIC-International Society of Thrombosis and Haemostasis (ISTH) score rather than the overt DIC-ISTH score appears to be more compatible with the profile of hypercoagulability in hospitalized COVID-19 patients. The scores for diagnosis of compensated and overt DIC are shown in Table II. In patients with compensated DIC-ISTH score >5 treatment with LMWH at intermediate dose should be considered. Therapeutic doses of LMWH should be considered if the levels of D-dimer continue to increase (i.e. doubling of D-dimer concentration or D-dimer levels higher than 10000 ng/ml). The bleeding risk needs to be carefully evaluated. In case of severe AT deficiency (<50%) administration of antithrombin concentrate should be considered.
- e. An overt DIC should be considered when the clotting times continue to prolong, and fibrinogen concentration and platelet count continues to decrease.

- **3. Prevention of VTE in patients with COVID-19** Patients with COVID-19 are classified at high risk for VTE principally because of the disease characteristics (severe stage, enhanced inflammation and hypercoagulability) and the frequent presence of inherent predisposing risk factors, particularly, cardiovascular diseases and cardiovascular risk factors (obesity, diabetes mellitus, arterial hypertension) or other underlying diseases. The risk of VTE is recognized (a) during hospitalization at the conventional ward or in ICU (b) after hospital discharge in high risk patients (c) in out-hospital setting, in patients with mild COVID-19 who receive home-based medical care.

- a. **Hospitalized patients** with vascular disease and COVID-19 are at high risk for VTE. LMWH at prophylactic, weight-adjusted dose or intermediate dose, in absence of contraindications or active bleeding is recommended for all patients including those with moderate renal insufficiency (creatinine clearance ≥ 30 ml/min), upon admission until hospital discharge.

A. Compensated DIC-ISTH score

Predictor	Thresholds	Score
Confirmed COVID-19	yes	2
Platelet count	$>100 \times 10^9$/L	0
	$<100 \times 10^9$/L	1
PT prolongation	<3 sec	0
	>3 sec	1
D-dimers	> of the upper normal limit adapted for the agecut-	0
	< of the upper normal limit adapted for the agecut-	1
Antithrombin activity	normal	0
	<lower normal limit	1
Protein C	normal	0
	<lower normal limit	1

B. Overt DIC-ISTH score

Predictor	Thresholds	Score
D-dimers	Strong increase (× 2 – 3)	3
	Moderate increase (× 1.5)	2
	No increase	0
Platelet count (× G/L)	<50	2
	50 - 100	1
	>100	0
Fibrinogen level (mg/dl)	<1.0	1
	≥1.0	0
Prothrombin time (sec)	>6 sec	2
	3 - 6 sec	1
	<3 sec	0

Table II *- Score for DIC diagnosis proposed by ISTH. DIC positive if the score is ≥ 5.*

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- i. In patients with severe renal failure (creatinine clearance <30 ml/ min), UFH is the first option for thromboprophylaxis. Due to the high frequency of heparin resistance the LMWH tinzaparin or dalteparin (which show limited accumulation in this context) at weight adjusted dose can be considered instead of UFH. In this case, peak and/or trough levels of anti-Xa activity in plasma should be monitored and the dose should be adapted in order to avoid any drug accumulation.
- ii. Levels of D-dimer should be monitored daily during hospitalization and the dose of LMWH should be increased to therapeutic levels in patients with important rising D-dimer (i.e. doubling of D-dimer concentration or D-dimer levels higher than 10000 ng/ml) after careful evaluation of bleeding risk. This strategy is considered of particular importance for ICU-patients.
- iii. Exploration of VTE with imaging methods could be considered in patients with sharp increase of D-dimer.

- b. **Patients with VD-CVR and COVID-19 who receive health care at home or in non-hospital structures** (i.e. retirement home) should be assessed for VTE risk using the IMPROVE score (accessible on line : https://www.outcomes-umassmed.org/ IMPROVE/risk_score/index.html).

- i. Patients at high risk for VTE with creatinine clearance ≥ 30 ml/min, can be considered for thromboprophylaxis with rivaroxaban 10 mg or betrixaban 80 mg once daily or LMWH at prophylactic weight-adjusted doses.
- ii. Rivaroxaban and betrixaban present some practical advantages over LMWH which are: simpler

administration mode which does not require nurse visits. Consequently, there is no risk of exposure of healthcare staff with contamination risk. Oral administration may improve patients' adherence to thromboprophylaxis.

- iii. In case that the patient receives home treatment with antiviral or other drugs that may alter the pharmacokinetics of DOACs, thromboprophylaxis with LMWH should be considered as first-line treatment.

- c. **Prevention of post-hospital discharge VTE in patients with VD-CVR and COVID-19**

- i. Systematic evaluation of VTE risk is recommended to all COVID-19 patients before hospital discharge using the IMPROVE-D-dimer score.
- ii. Patients at high VTE risk after discharge with creatinine clearance # 30 ml/min, can be considered for thromboprophylaxis with rivaroxaban 10 mg or betrixaban 80 mg once daily p.o. or prophylactic weight-adjusted doses of LMWH for 40 days.

Treatment of VTE in patients with vascular disease or cardiovascular risk factors hospitalized with COVID-19

For hospitalized patients with VD-CVR and COVID-19 VAS endorses the recommendations of the ISTH Scientific Subcommittee for diagnosis and treatment of VTE.

Conclusion

Vascular patients and citizens with cardiovascular risk factors are at high risk for COVID-19 worsening and should be placed at the center of the medical care during the SARS-CoV-2 pandemic. Prevention of SARS-CoV-2 infection, Detection of patients with COVID-19 at high risk of disease worsening and Anticipation of the vascular complications related with the inflammatory storm and hypercoagulability is the new strategy proposed by the VAS. The strategy proposed by VAS focusing on vascular patients and citizens with cardiovascular risk factors as schematically represented in Figure 1, is expected to contribute in the control of the vascular complications of COVID-19 and the decrease of the flow of these patients towards the intensive care units. The Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19 published by the VAS-European Independent Foundation in Angiology/Vascular Medicine involved 74 experts on vascular disease, blood coagulation disorders and antithrombotic treatment. Specialists on angiology and vascular medicine, hematology, immunology, cardiology, internal medicine, vascular surgery and cardiothoracic surgery, anesthesiology and intensive care from 31 countries from Asia, Oceania, Europe, North and South America and Africa participated in this project. The VAS-European Independent Foundation in Angiology/Vascular Medicine is an established international organization in co-operation with Universities, Hospitals, International and National Scientific Societies, the World Health Organization and the European Union and undertakes the implementation of the guidelines through a large network of physicians from the primary to the trietery health care worldwide. The network needs also to obtain an active, continue involvement of patients in disease control. To this aim VAS has elaborated an educational campaign targeting the patients with cardiovascular disease and the citizens with cardiovascular risk factors and involving the actors in the primary health care, from the public and private sector.

Endnotes

[i] The term "*patients with vascular disease or cardiovascular risk factors*" (VD-CVR) refers to patients with personal history of arteriopathy or arterial thrombosis, including patients with history of ischemic stroke, carotid artery disease, coronary artery disease, peripheral artery disease (PAD), or arterial thrombosis of rare localization (i.e. mesenteric artery thrombosis), patients with history of DVT, PE, or vein thrombosis of rare localization (i.e. cerebral vein thrombosis, splanchnic vein thrombosis, upper limb thrombosis). Obese individuals (BMI>30), and patients with diabetes mellitus or arterial hypertension are also included.

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