Letter to the Editor

Can COVID19 trigger the plaque vulnerability—a Kounis syndrome warning for "asymptomatic subjects"

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The global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1) represents a one-in-a-lifetime, worldwide health crisis with 11,638,136 confirmed cases worldwide since the beginning of the epidemic and 538,266 fatalities (4.63% lethality) (Data provided by the WHO Health Emergency Dashboard on May 10th, 10.00 am CET).

The key clinical features observed in patients affected by SARS-CoV-2 are related to lower respiratory tract illness with fever, dry cough, and dyspnea. Recent evidence shows that those patients have a disproportionately higher incidence of cerebral ischemic stroke and myocardial infarction (2-5).

The pathophysiology of the SARS-CoV-2 is not yet fully understood but recent studies suggest that the virus gains entry into the host through the use of angiotensin-converting enzyme 2 (ACE2) as its cellular receptor. ACE2 is a membrane-bound mono-carboxypeptidase found ubiquitously in humans in the type II pneumocytes of the lungs, in the kidneys, in the intestine but also in cardiomyocytes, coronary pericytes and coronary endothelial cells (6). ACE2 plays a counterbalancing role in the renin angiotensin-converting system (RAAS) and is a carboxypeptidase that converts angiotensin II (Ang II) into angiotensin 1-7 (Ang 1-7). The loss of ACE2, caused by the SARS-CoV-2 at the cell surface, leads to (I) a decrease in the levels of cardioprotective (Ang 1-7) and (II) an increase in the levels of Ang II, which promotes endothelial dysfunction and inflammation, and promote atherogenesis (7). ACE2 plays an important role in the molecular pathways implicated in the development of carotid and coronary atherosclerotic plaques (8,9). In *Figure 1*, the consequences of the dysregulation of the renin-angiotensin system caused by the SARS-CoV-2 inside atherosclerotic plaques are illustrated: endothelial dysfunction, leading to thrombosis (10); enhanced permeability of the endothelial barrier, favouring the invasion of the plaque by inflammatory cells and the insurgence of intra-plaque haemorrhage (IPH); accumulation of inflammatory cells, including neutrophils, activated monocytes, lymphocytes and plasma cells in the plaque. The pro-inflammatory and pro-thrombotic activity of angiotensin II might transform a vulnerable plaque into a ruptured and complicated plaque. The ACE2 pathway alterations promote the development of vascular diseases associated with Ang-II-mediated vascular inflammation and activation of the c-Jun N-terminal kinase (JNK) signalling, leading to the notion that ACE2 demodulation reduces protection against vascular diseases (11,12).

Recent exploration of the pulmonary immunopathology and microvascular coagulopathy associated with SARS-CoV-2 infection also suggest an enhanced activation of the immune system similar to the macrophage-activation syndrome that may unmask subclinical cardiovascular disease13, potentially also promoting destabilizing intraplaque inflammation. Although the precise stimuli

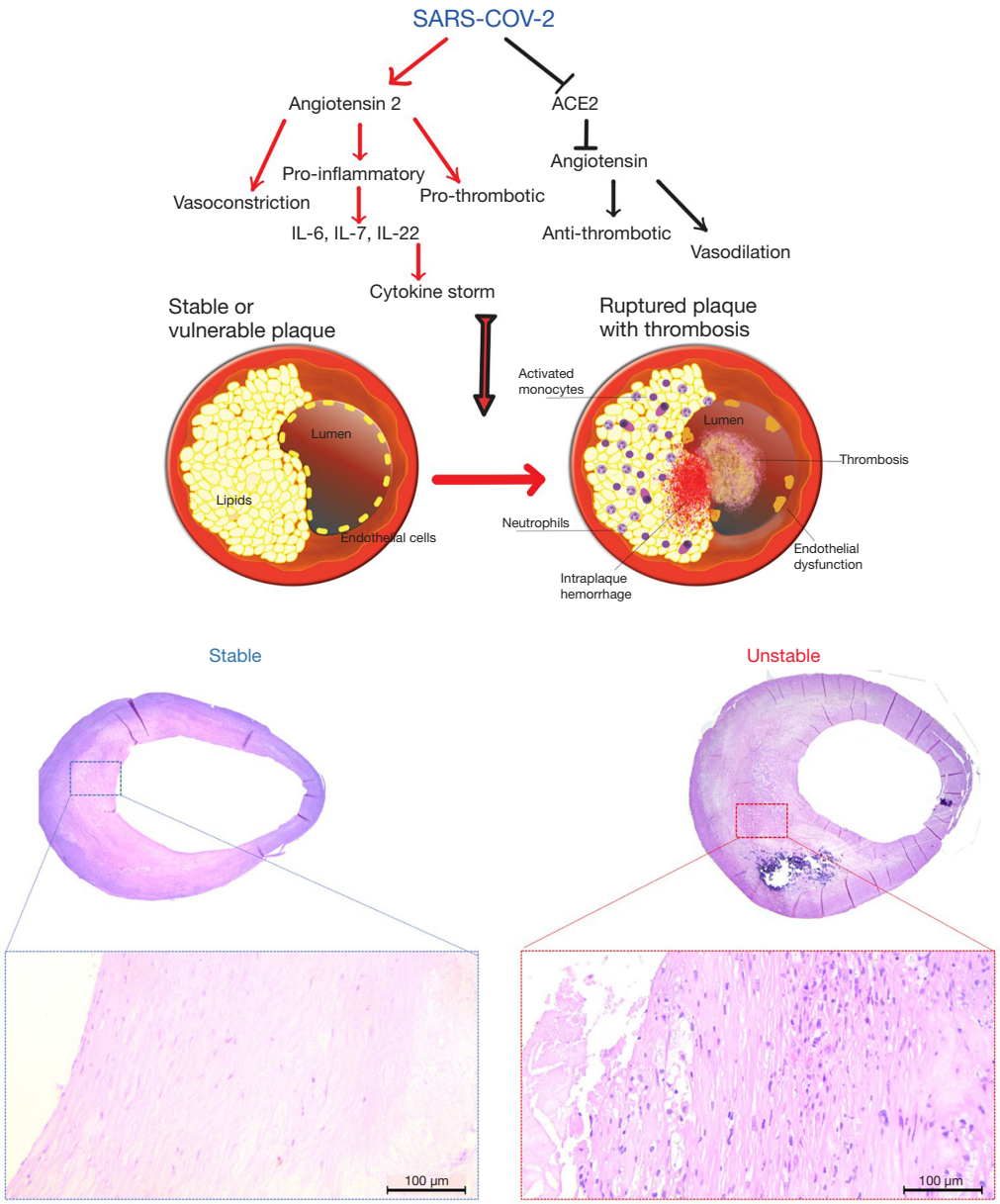

Figure 1 XXXXXXXXXXXXXXXXXXXXXXX

that trigger atherosclerotic plaque instability have not yet been identified, 'Kounis syndrome', myocardial infarction from massive activation of inflammation in anaphylaxis, exemplifies another association between an (extreme) inflammatory stimuli, plaque instability and atherothrombosis (14). COVID appears to be associated with often very vigorous inflammatory response/storm and clinical intervention in patients with COVID-19 has demonstrated a strong upregulation of cytokine production in those subjects who are critically ill with SARS-CoV2-induced pneumonia. The secretion of multiple cytokines, also termed Cytokine Release Syndrome (CRS), is closely related to development of clinical symptoms. In particular, the interferons (IFNs) that play the central role in innate immunity to viruses and other microbial pathogens, the interleukins (ILs) that regulate the immune cell differentiation and activation, and the chemokines that bind to one or more of 21 G-protein-coupled receptors

and constitute the pathophysiologic substrate of Kounis anaphylaxis associated syndrome could be new therapeutic targets of Covid-19 infection

Based on these pathophysiological mechanisms, it appears possible that subjects infected with SARS-CoV-2 suffer an increased risk of conversion from asymptomatic, subclinical, atherosclerotic disease15 into an unstable state with vulnerable plaques in the carotid and/or coronary arteries due to the immunopathology associated with the viral infection. Interestingly, Europe and US hospitals have seen a drop in admissions for acute myocardial infarction. Some EU countries showed a reduction of cardiac catheterization procedures of 48%, with a reduction of 40% for primary angioplasty and similar results have been reported in the USA (16,17). However, this is matter of debate and it is hypothesized that it is due to the delay in seeking for care by the patients.

This hypothesis would also explain the increased prevalence of ischemic events12 in young subjects, *asymptomatic* for lower respiratory tract illness, who have developed unexpected occurrence of ischemic events consistent with large-vessel stroke.

In conclusion, we hypothesize that SARS-CoV-2 has the potential to trigger cellular and molecular processes in coronary and carotid atherosclerotic lesions promote an increased vulnerability with subsequent increased risk of cerebral ischemic stroke or myocardial infarction. If this hypothesis would be demonstrated, it could suggest using protective approaches for plaque protection in subjects affected by SARS-CoV-2 with special attention to medical therapy for cardiovascular disease, including an antithrombotic preventive approach (18) and potentially also therapy targeting immune pathways operating in the disease, once these have been unravelled (19).

Moreover, this would have a significant clinical implication for high-risk category patients in whom Covid-19 may be severe or fatal. These include the elderly (>60 years old), obese patients, diabetic patients, smokers and patients with hypertension and cardiovascular disease, all categories at higher risk for developing atherosclerosis too. These patients, if positive for SARS-CoV-2 even if asymptomatic, could be at increased risk of developing cerebral ischemic strokes, and myocardial infarction due to increased instability of coronary and carotid plaques.

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Footnote

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