In any event, the use of clinical indexes and high-sensitivity troponin does not completely eliminate the need for functional or anatomical tests to detect coronary disease in a part of the population referred to a chest pain unit, and in our opinion, none of the factors mentioned affects the validity of the results of our study.

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The use of antiplatelet agents for arterial thromboprophylaxis in COVID-19

El uso de agentes antiplaquetarios para la tromboprofilaxis arterial en la COVID-19

To the Editor,

We read with interest the retrospective study reported by Rey et al.[1] to describe the clinical characteristics and outcomes of patients with novel coronavirus disease 2019 (COVID-19) who developed acute arterial thrombosis. Despite being a small-scale study (n = 87), there are a few clinical trends to be noted. Based on the reported findings, we observed that the proportion of COVID-19 patients with major cardiovascular risk factors who developed acute arterial thrombosis is higher than that of their non-COVID-19 counterparts. Such finding hinted at the possibility that thromboinflammation plays a greater role for the development of arterial thrombosis in COVID-19 patients than traditional cardiovascular risk factors. In addition, the mortality rate of COVID-19 patients with arterial thrombosis was high (44.7%), which indicates a poor prognosis. Therefore, we would like to propose routine antiplatelet therapy (low-dose aspirin, clopidogrel, ticagrelor, prasugrel, ticlopidine, and dipyridamole) for arterial thromboprophylaxis in COVID-19 patients who are deemed at heightened risk for the development of acute arterial thrombosis.

Low-dose aspirin (75–150 mg/d) is sufficient to irreversibly acetylate Ser 530 of COX-1, thus preferentially inhibiting platelet generation of thromboxane A_2, and interfering with the formation of arterial thrombus. On the other hand, for $P2Y_{12}$ inhibitors (clopidogrel, ticagrelor, prasugrel, and ticlopidine), either the parent drug or the active metabolite blocks the $P2Y_{12}$ component of adenosine diphosphate receptors on the platelet surface, which prevents activation of the glycoprotein IIb/IIIa receptor complex, thereby reducing platelet aggregation and subsequent arterial thrombus formation. Dipyridamole inhibits the activity of adenosine deaminase and phosphodiesterase, which causes an accumulation of adenosine, adenine nucleotides, and cyclic AMP; these mediators then inhibit platelet aggregation and the subsequent arterial thrombus formation. Aspirin and dipyridamole may be particularly favored in COVID-19 patients; aspirin possesses antiviral activity related to its ability to inhibit the coronavirus-induced nuclear factor kappa B pathway,[2] while dipyridamole appears to directly suppress severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of COVID-19 based on in silico docking analysis and in vitro cell culture study.[3]

There have been limited studies that have demonstrated favorable clinical outcomes in COVID-19 with the use of antiplatelet therapy either alone or in combination with an anticoagulant. In their prospective observational study among critically ill patients with COVID-19, Ranucci et al.[4] reported that a combination of an enhanced prophylactic dose of heparin, clopidogrel, and antithrombin correction returned the parameters of viscoelastic coagulation tests to essentially normal (129). In a proof-of-concept, case control, phase IIb study in 5 patients with COVID-19 and severe respiratory failure treated with a combination of tirofiban, aspirin, clopidogrel, and fondaparinux, Viecca et al.[5] reported superiority in terms of improvement in oxygenation, and weaning time from continuous positive airway pressure therapy compared with controls matched for disease severity who received either prophylactic or treatment-dose heparin. Liu et al.[3] performed a multicenter, parallel, randomized controlled trial of 31 patients with COVID-19 with severe or critical illness, who received either standard of care (n = 17) or dipyridamole at a dose of 50 mg 3 times daily for 14 days in addition to the standard of care (n = 14). Patients randomized to dipyridamole had an increased survival and remission rate that approached statistical significance (odds ratio, 23.75; 95% confidence interval, 0.87-648; $P = .06$), as well as reduced D-dimer levels, and increased lymphocyte and platelet counts.

Nevertheless, at the time of writing, we are not aware of any studies that have reported the outcomes on the use of antiplatelet agents for the prevention of arterial thrombotic events in patients with COVID-19. We urge the performance of a study to evaluate the use of antiplatelet therapy to prevent arterial thrombotic events,

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which can be fatal in patients with COVID-19. In the meantime, antiplatelet therapy can be prudently administered to critically ill patients with COVID-19 who are at high risk of thromboinflammation but low risk of bleeding. With more studies available in the future, we could then identify the population of patients with COVID-19 most likely to benefit from the use of antiplatelet therapy to prevent the occurrence of arterial or even venous thrombotic events.

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A new inflammatory-microthrombotic syndrome as an explanation for thrombotic complications in patients with COVID-19

Un nuevo síndrome inflamatorio-microtrombótico como explicación para las complicaciones trombóticas en pacientes con COVID-19

To the Editor,

We have read with great interest the article by King et al.[1] recently published in *Revista Española de Cardiología*. In this article, the authors discuss the higher incidence of thrombotic events in multiple territories and a higher International Society on Thrombosis and Haemostasis (ISTH) disseminated intravascular coagulation (DIC) score in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although the authors mention that they have not ruled out a pre-existing prothrombotic state, our group, consistent with what the authors described,[2] has proposed a possible role of endothelial injury, complement, and coagulation in the pathogenesis of coronavirus disease 2019 (COVID-19).[3]

Our pathogenic scheme is based on the similarity of certain clinical and histopathologic findings of various entities that have thrombotic microangiopathy in common with COVID-19, and it postulates that the damage induced by this disease has an endothelial origin with 2 pathogenic routes: an inflammatory route, with predominance of the "cytokine storm" component, and a microangiopathic route involving the complement system.[3]

Furthermore, endothelial involvement could lead to platelet activation, thus altering coagulation and causing DIC, as described by the authors of the article. This fact *per se* could increase thrombin and prothrombin and trigger complement activation through C5.[4]

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For instance, thrombotic microangiopathy has been reported in a patient with severe COVID-19, indicating a pathogenic relationship between these conditions.[5] The potential role of ADAMTS13 deficiency in serious forms of the disease is another possible factor, as described by Huisman et al.[6] in a recent article.

Additionally, the inflammatory route itself could activate complement through certain neutrophil serine proteases and macrophages.[7] Consequently, we believe that there is a strong relationship between inflammation, complement, thrombotic microangiopathy, and coagulation in the pathogenesis of COVID-19. This may represent a new COVID-19–related inflammatory-microthrombotic syndrome which could explain the authors' interesting findings.[2–4]

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