In Response

Maier et al,[1] in their letter, nicely address an important issue that is of clinical relevance not just for Coronavirus Disease 2019 (COVID-19) patients, but in every case of hyperfibrinogenemia (inflammatory reactions, extracorporeal membrane oxygenation, etc). The observation that under argatroban treatment, the Clauss determination of fibrinogen levels may provide a gross underestimation is not new,[2] but certainly deserves to be underlined in the setting of COVID-19 patients, where hyperfibrinogenemia is a common finding.[3] Recently, in a series of patients with COVID-19–related acute respiratory distress syndrome, we could find a median value of fibrinogen at the admission in the intensive care unit of 794 mg/dL (interquartile range, 583–933 mg/dL).[4]

The mechanism by which the conventional Clauss measure of fibrinogen levels may falsely underestimate the fibrinogen levels in patients under argatroban has been well elucidated by the authors and basically derives from the direct inhibition of the thrombin present in Clauss reagents. However, this effect is different in different commercially available assays, ranging from a 23% to 29% reduction to a 96% reduction.[2] Of notice, 3 of the reagents tested in the study of Zhang et al[2] (STA-fibrinogen, Diagnostica Stago, Asnieres, France; Siemens Thrombin, Siemens Healthcare, Marburg, Germany; and RecombiPlas Tin 2G, Instrumentation Laboratory, Boston, MA) did not show any significant reduction in fibrinogen levels for an activated partial thromboplastin time (aPTT) ratio <3.0. Since the usual aPTT ratio during argatroban therapy ranges between 1.5 and 2.0, the measure of fibrinogen is not necessarily biased when using Clauss reagents appropriate for patients under argatroban.

There is a second direct thrombin inhibitor (bivalirudin) that may suffer from a similar problem. Again, the potential underestimation of fibrinogen levels is strongly dependent on the type of reagent, with a Stago-manufactured reagent (STA-R Evolution) that is insensitive to bivalirudin concentration unless for very high doses.[5]

Currently, there are various types of viscoelastic tests (VET) that allow a fibrinogen evaluation by skipping the platelet contribution to clot strength. These tests are insensitive to the action of argatroban and bivalirudin,[5] and the authors of this letter advocate their use for functional fibrinogen assessment in the presence of argatroban. I am certainly a supporter of VET in this and other scenarios, and we did use VET in our recently published study[4] as well as in other studies in patients on bivalirudin treatment.[6] However, I think that clinicians should be aware of the strengths and weaknesses of the various tests and of the fact that, depending on the kind of reagent used to skip the platelet contribution to clot strength, the VET themselves may provide an incorrect estimation of the fibrinogen contribution to clot strength.[7]

In the presence of an unexplained fall of Clauss fibrinogen levels after starting argatroban (or bivalirudin) treatment, it is certainly reasonable to double-check the fibrinogen contribution to clot strength using VET, as the authors did in their report.

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