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COMMENTARY

To escalate thromboprophylacic heparin intensity in COVID-19 or not? That is still the question

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Since the first few weeks of the coronavirus disease 2019 (COVID-19) pandemic, venous thromboembolism (VTE) and arterial thromboembolic events were recognized among the main complications of COVID-19.[1-3] A series of pathobiological mechanisms that contribute to hypercoagulability, endothelial dysfunction, and stasis were proposed.[4,5] Early studies also suggested an association between use of prophylactic anticoagulation, in some series with escalated dosing, and lower rates of mortality or decompensation. These observations ignited the search for effective ways to reduce the risks of microthrombosis and macrothrombosis, and improving patient outcomes in COVID-19. Therefore, dozens of randomized controlled trials (RCTs) using conventional or novel antithrombotic agents were designed to minimize rates of thrombosis, or improve outcomes such as need for organ support or mortality.[6-8] Besides the differences in study interventions, there is heterogeneity with respect to care setting and enrollment criteria, as well as the choice of primary and secondary outcomes in these trials.

Some of these RCTs were recently completed and shared their findings. Among outpatients, the ACTIV-4B trial enrolled relatively low-risk patients and found low event rates for hospitalizations, thrombotic events, or mortality, without a major difference in patients randomly assigned to low-dose aspirin, low-intensity apixaban, full-intensity apixaban, or placebo.[9] A relatively small placebo-controlled RCT of sulodexide,[10] an oral glycosaminoglycan that contains heparan sulfate and dermatan sulfate,[11] was potentially suggestive of reduction in D-dimer and inflammatory markers, as well as hospitalizations. However, the study was not definitive due to relatively small sample size, postrandomization exclusions in main analyses, lack of complete blinding, and others. Among outpatients following hospital discharge for COVID-19, the MICHELLE trial was recently published.[12] Despite a relatively small sample, the study suggested a potential for reduction in symptomatic or asymptomatic, screening-based VTE or cardiovascular death in those receiving rivaroxaban 10 mg daily for 35 days compared to no anticoagulation.

Hospitalized patients with COVID-19 are at higher risk of thrombotic events. Patients admitted to the intensive care unit (ICU) are the highest-risk population. Among hospitalized patients, there is greater uncertainty and controversy about the ideal thromboprophylactic strategy.[4,13-16] Antiplatelet therapy with aspirin or $P2Y_{12}$ inhibitors did not bear favorable results in hospitalized patients (RECOVERY[17] and ACTIV-4A[18]). Multiple RCTs failed to show a net benefit from prophylaxis with either intermediate-intensity anticoagulation[19,20] or full-intensity anticoagulation[21] compared with standard-dose prophylaxis.

Among hospitalized non-ICU patients, the ACTION trial did not suggest benefit for full-intensity rivaroxaban.[22] Results from the multiplatform trial,[23] the RAPID trial,[24] and the HEP-COVID trial,[25] despite some heterogeneity in design and reporting, are suggestive of a

reduction in thrombotic events and a potential for reduced mortality among non-ICU hospitalized patients (Figure 1) who received full-intensity anticoagulation compared with control. These findings resulted in recommendations in practice guidelines in carefully selected patients, including those by the ISTH, the American College of Chest Physicians, and the American Society of Hematology.[14-16] Findings from some other RCTs were different. Therefore, additional trial results would be of great importance to improve our understanding.

In this context of continued interest in RCT data, the Swiss COVID-Hep trial by Blondon et al[26] in this issue of *Research and Practice in Thrombosis and Haemostasis* is a timely contribution. In this multicenter RCT of hospitalized patients with COVID-19 who had elevated D-dimer >1000 ng/mL or were admitted to stepdown units/ICUs, patients were randomly assigned to in-hospital full-intensity anticoagulation versus lower intensity of anticoagulation. The latter consisted of standard-dose prophylactic anticoagulation in patients admitted to hospital wards, and intermediate-dose anticoagulation in patients admitted to stepdown units/ICUs. The primary outcome, a composite of all-cause mortality, VTE, arterial thrombosis, and disseminated intravascular coagulopathy, occurred in 5.4% of participants assigned to full-intensity anticoagulation compared with 5.0% of those assigned to control. The main analysis, with some protocol amendments, was adjusted and reported a hazard ratio (HR) of 0.76 (95% confidence interval [CI], 0.18-3.21). Importantly, despite screening for deep vein thrombosis by routine imaging, there were no events in hospitalized ward patients. Three deaths were reported in each arm of the trial. In addition, the study also reports provocative findings among the subgroup who were not using invasive mechanical ventilation. The authors reported an increased hazard of 30-day death or invasive mechanical ventilation in those assigned to full-intensity anticoagulation versus control (adjusted HR, 4.10, 95% CI, 1.40-12.03). The trial was prematurely terminated due to slow recruitment.

On a first look, the low event rate and findings that are discordant to some other completed RCTs draw one's attention. A closer look, however, brings additional insights to put these results in context. First, the sample size estimates were based on the data early during the pandemic and, in retrospect, overestimated the event rates and a potential treatment effect. Second, in some patients, the study intervention was withheld if they did not require organ (oxygen) support, although this was not a part of the primary "endpoint." Third, for understandable reasons, the study was terminated prematurely. Fourth, subgroup analyses not adjusted for multiplicity of comparisons should be interpreted with caution.

These issues notwithstanding, Blondon et al[26] should be commended for completing another important trial. Trial recruitment continued for a longer duration than some of the other previously completed RCTs. It can be hypothesized that in more contemporary cohorts of COVID-19, for a wide range of reasons including more frequent use of therapies against (thrombo)inflammation, thrombotic event rates are lower than prior months. In addition, the trialists had made a priori determination not to include less ominous forms of VTE (such as distal deep vein thrombosis, subsegmental pulmonary embolism, or catheter-associated VTE) as part of the primary outcome. In addition, it should be kept in mind that some form of investigation excluded pulmonary (thrombo)embolism in the majority of Swiss COVID-Hep participants before enrollment. Considering all the above issues, Swiss COVID-Hep results should be seen as complementary but not necessarily contradictory to prior RCTs.

Where do we go from here? Findings from other RCTs,[7,8] particularly FREEDOM-COVID-19[27]—the largest of these trials—are anxiously awaited. It is possible that we should attune the thromboprophylactic strategies based on acuity of illness, sex, viral variants, biomarkers such as D-dimer, cotreatments (particularly anti-inflammatory therapies) and also based on whether thrombosis has already been assessed and excluded upon admission. Some efforts are under way to pool the results of the completed RCTs at the study level[28] and at the individual patient level. Such analyses will provide better statistical power and granularity (with individual patient data) to tease out the nuances of treatment effects for these preventative strategies in patients with COVID-19. Time will tell. Until then, the work by Blondon et al[26] has

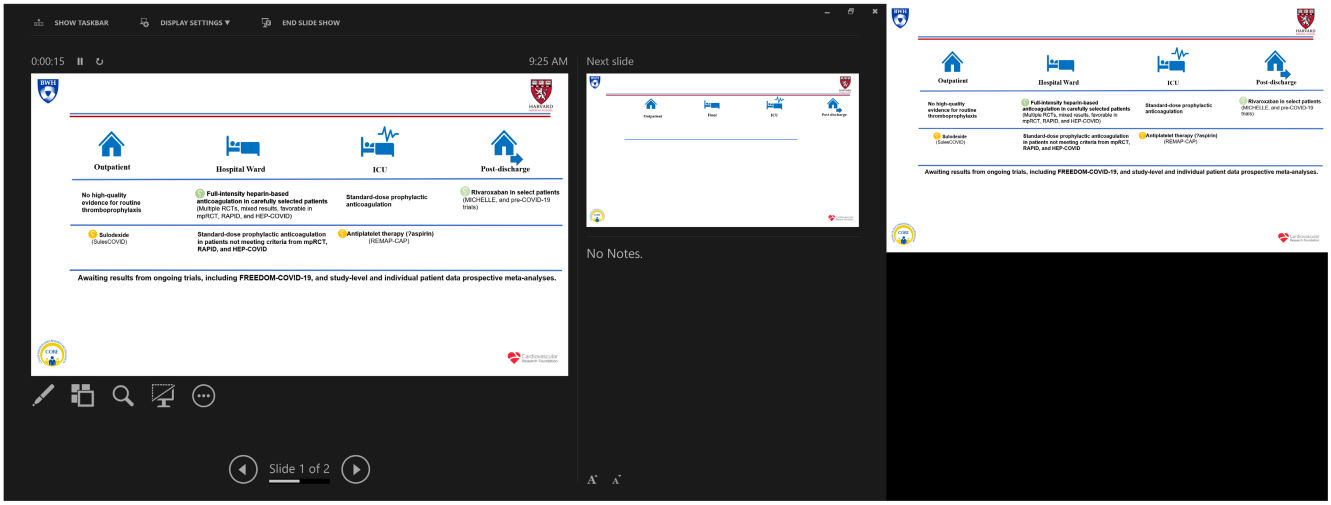

FIGURE 1 Thromboprophylaxis for COVID-19 based on data from completed randomized trials

opened new horizons in our understanding of COVID-19–associated thrombosis and prophylaxis against it.

RELATIONSHIP DISCLOSURE

The author reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two brand models of inferior vena cava filters.

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