EDITORIAL

Surviving Covid-19 with Heparin?

Hugo ten Cate, M.D., Ph.D.

Patients who are admitted to the hospital with coronavirus disease 2019 (Covid-19) are at high risk for thrombosis, particularly venous thromboembolism (VTE). In a meta-analysis of 66 studies, the overall prevalence of VTE among patients with Covid-19 was 14.1%, with the highest incidence (22.7%) among those admitted to intensive care units (ICUs).[1] Systemic hypercoagulability is a feature of Covid-19, and early studies have shown an association between plasma D-dimer levels and survival.[2] These data have prompted a search for better thrombosis prevention, considering that the high frequencies of VTE occurred in patients who were already receiving standard thromboprophylaxis, mostly with low-molecular-weight heparin (LMWH). So the question arises: would higher doses be more effective and still be safe?

Among 75 registered clinical trials of different antithrombotic strategies with different agents in patients with Covid-19, a majority have involved the use of heparin or LMWH.[3] The INSPIRATION trial, which compared intermediate doses of LMWH with standard-dose prophylaxis in 562 patients who were being treated in an ICU, showed no between-group difference in the primary outcome (a composite of adjudicated acute VTE, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or death) but more bleeding in the intermediate-dose group.[4] In a preprint article, the authors reported the findings of the RAPID trial, which evaluated therapeutic heparin as compared with prophylactic heparin or LMWH in 465 patients who were not critically ill.[5] In that trial, there was also no difference between groups in the primary outcome (a composite of ICU admission, noninvasive or invasive mechanical ventilation, or death), but the therapeutic anticoagulation group had a lower incidence of death at 28 days.

Now reported in the *Journal* are the results of an international, multiplatform, randomized clinical trial that combined data from patients who were enrolled in one conventional randomized trial (ACTIV-4a) and in two trials that used response-adaptive randomization (REMAP-CAP and ATTACC).[6,7] One article focuses on patients with severe illness and the other on those with moderate illness. In the two articles, the potential benefits and risks of therapeutic-dose heparin or LMWH (with the latter being used in >90% of the patients in both groups) are assessed against standard thromboprophylaxis. The main findings were that therapeutic-dose heparin or LMWH did not improve the primary outcome of days without organ support in the critically ill patients and was associated with more major bleeding complications than usual-care prophylaxis (3.8% vs. 2.3%). In contrast, in the moderately ill patients, therapeutic-dose heparin or LMWH appeared to increase the probability of survival until hospital discharge with a reduced need for organ support. However, among the patients with moderate illness, more major bleeding occurred with heparin or LMWH than with thromboprophylaxis (1.9% vs. 0.9%).

How can we reconcile these different outcomes in different populations? One factor may be that in the critically ill patients, the underlying thrombotic and inflammatory damage may have been too advanced to have been influenced by higher doses of heparins. In severe Covid-19, thrombus formation is driven by an orchestra of cytokines, activated complement, platelets, endothelial and inflammatory cells, and microvesicles that provide an efficient catalytic surface for clot-

ting reactions.[8] These surface-bound complexes and fibrin-bound thrombin are quite resistant to inhibition by antithrombin, the key cofactor in heparin and LMWH. If we assume that such mechanisms are slightly less active in patients with moderate disease, it could help to explain the observed benefit of thromboprophylaxis in the noncritically ill patients.

Other causes for the different findings may relate to the differences in populations. Although the vast majority of critically ill patients were recruited in centers that were running the REMAP-CAP trial in the United Kingdom, the patients with moderate disease were recruited mostly from the ATTACC and ACTIV-4a trials in the United States and Brazil. These populations differ not only geographically but also ethnically. Next, there are caveats related to the nonconcurrent nature of the control group in the platform trial, in which experimental groups entered and exited the trial at different times.[9] Although the authors included adjustments for the enrollment period (in 2-week intervals) in their models, such adjustment may not have fully corrected for differences that are not observed in conventional randomized, controlled trials. Furthermore, the method of standard prophylaxis was left to the discretion of the physicians, which resulted in a mix of conventional prophylaxis doses and intermediate doses within the treatment groups. Thus, in the trial involving critically ill patients, 22.4% of those in the therapeutic-dose group did not receive a therapeutic dose, whereas 51.7% of those in the control group received an intermediate dose — a factor that may have diluted any benefit of therapeutic-dose anticoagulation. This issue was somewhat less important in the trial involving patients with moderate disease, in which 20.4% of the therapeutic-dose group did not receive a therapeutic dose, whereas 26.5% in the control group received an intermediate dose.

With the preceding caveats, what conclusions can be drawn from these mixed data? First, the available evidence does not support use of therapeutic-dose heparin or LMWH for thrombosis prevention in critically ill patients. Other antithrombotic or even profibrinolytic strategies may be warranted. Second, whether intermediate or therapeutic doses of thromboprophylactic drugs are effective and safe in moderately ill patients with Covid-19 remains an important question.

In spite of the signals of benefit of anticoagulation in noncritically ill patients with Covid-19, physicians must deal with the key issues regarding the lack of insight into the mechanisms by which heparin or LMWH does (or does not) provide protection and the question of whether the individual patient's bleeding risk outweighs the benefit. As the late Ed Salzman concluded in the early days of clinical research with LMWH: "a promising innovation in antithrombotic treatment, but the jury is still out."[10]

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Thrombosis Expertise Center, Department of Internal Medicine, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands, and the Center for Thrombosis and Hemostasis, Gutenberg University Medical Center, Mainz, Germany.

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