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COMMENTARY

First do no harm

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For prevention of thrombotic events in patients hospitalized because of COVID-19, low molecular weight heparin (LMWH) and unfractionated heparin are the rational anticoagulants of choice, given that the overall majority of thromboses are of venous origin.[1-3] In view of the high incidence of venous thromboembolism in ward and in intensive care unit (ICU) patients, a plethora of 75 studies have been registered since the start of the COVID pandemic.[4] The majority of these compared therapeutic doses, and to a lesser extent, intermediate doses, versus a standard prophylactic dosis of LMWH in two sets of hospitalized COVID-19 patients (i.e., ward patients who were named moderately or not critically ill and ICU patients). In this issue, Sholzberg et al. performed a meta-analysis supporting the potential benefit of therapeutic LMWH in moderately ill patients.[5] However, limitations in the trials of this meta-analysis exist, and this may lead to severe limitations when taken together.

The INSPIRATION study, comparing intermediate doses of LMWH with standard-dose prophylaxis in ICU patients with COVID-19, showed no difference between the two groups in the primary composite outcome of adjudicated acute venous thromboembolism, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or death, but more bleeding occurred in the intermediate-dose group.[6]

In the RAPID trial, evaluating therapeutic LMWH versus standard prophylactic LMWH in noncritically ill patients with COVID-19, the primary outcome showed no difference between the groups in the primary composite outcome, which were ICU admission, noninvasive or invasive mechanical ventilation, or death.[7] Surprisingly, a lower incidence of death, albeit with very wide confidence limits occurred in the therapeutic anticoagulation group at 28 days and, as surprisingly and seemingly counterintuitive, was a notable lower incidence of major bleeding in the patients receiving therapeutic anticoagulation.

In a so-called multiplatform, randomized clinical, data were combined from patients from the ACTIV-4a, a conventional randomized trial, and from patients of REMAP-CAP and ATTACC, two trials using a response-adaptive randomization.[8,9] Allocation was to either therapeutic or standard thromboprophylaxis with heparin or LMWH (the latter used in >90% in both groups). In critically ill patients, therapeutic heparin or LMWH did not improve the primary outcome of days without organ support and was associated with more major bleeding complications than standard thromboprophylaxis (3.8% vs. 2.3%). In the moderately ill patients, therapeutic-dose heparin or LMWH appeared to increase the probability of survival until hospital discharge and a reduced need for organ support; more major bleeding also occurred with therapeutic heparin or LMWH than with thromboprophylaxis (1.9% vs. 0.9%) and the median number of organ support-free days was the same in both treatment arms. Two factors may have led to the flawed results of this platform endeavor. First, in the control group, nonconcurrent patients were included, leading to potential spurious effects in the intervention group.[10] Second, in the 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, leading to a potential

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dilution of benefit of therapeutic-dose anticoagulation. In the patients with moderate disease, 20.4% of the therapeutic-dose group did not receive a therapeutic dose, whereas 26.5% in the control group received an intermediate dose.

In the HEP-COVID study of highly selective ward or ICU COVID-19 patients, with high risk based on D-dimer levels more than four times upper limit of normal,[11] therapeutic heparin led to a reduction in the primary composite outcome, consisting of venous thromboembolism detected by screening imaging tests or by imaging upon symptoms, arterial thromboembolism, or death, compared with standard prophylaxis (41.9% vs. 28.7%), including a reduction in venous thromboembolism (29.0% vs. 10.9%). This, however, was at the cost of more major bleeding (4.7% vs. 1.6%). The reduction in the primary endpoint was seen in non-ICU patients, but not in ICU patients. Taken together, these studies all seem to point toward a potential beneficial effect of therapeutically dosed LMWH over prophylactic or intermediate-dose LMWH in moderately ill patients with COVID-19. However, a closer look at these published studies reveals important methodological limitations to consider. First, all studies used an open-label trial design, associated with (potential) bias in the assessment of endpoints (e.g., the threshold to order diagnostic tests for suspected venous thromboembolism). Second, selected patients were included at a (very) slow accrual rate, mostly excluding patients with a higher risk of bleeding. Third, there was a large heterogeneity among the studies with respect to the chosen composite primary endpoint, but also to the incidence of comparable outcomes and the odds ratio of the effect of therapeutic LMWH. For instance, the odds ratio of mortality in moderately ill patients ranged across the studies between 0.22 and 0.82, that of major thrombotic events between 0.17 and 0.52, and that of and major bleeding between 0.52 and 1.8. Following these points back to the individual studies, the heterogeneity between the studies selected for inclusion in the meta-analysis published in this issue of the journal is considerable, which makes us question whether pooling of the data is valid.[5] The interpretation of the pooled overall effects observed in this meta-analysis are therefore surprising and debatable. The authors state that therapeutic heparin is beneficial in moderately ill ward patients but not in severely ill patients hospitalized with COVID-19. This conclusion is derived from a post hoc constructed definition of different endpoints that were not predefined in the individual studies. By combining elements of the included studies (e.g., death or (mechanical) ventilation, death or thrombotic complications), they observed a reduction of these complications in favor of therapeutic heparin in the moderately ill patients, whereas this was not seen in critically ill patients.

Importantly, in 2022, we live in a completely different COVID-19 environment, in which the current dominant omicron variant involving less severe disease, as well as the standard use of dexamethasone and interleukin-6 inhibitors, whereas many if not most patients included in the randomized controlled trials included in the meta-analysis became ill during the "first" wave and did not receive such treatment. Taking this latter consideration into account and added to the major limitations of both the methodology of the studies as well as the analytical methods used in this meta-analysis, the conclusion that therapeutic LMWH is beneficial to ward COVID-19 patients is too far-reaching. The very limited strength of evidence calls for more prudent conclusions and recommendations for clinical practice while waiting for more definitive studies to be published. This is reflected by the very prudent recommendations, based on nonunanimous voting, in the most recent version of the ASH COVID-19 thromboprophylaxis guidelines recommendations.[5] For ward patients with COVID-19, the evidence provided to inform therapeutic heparin is not firm enough. After all, when in doubt and in the absence of convincing evidence, *primum non nocere* remains the best guideline.

RELATIONSHIP DISCLOSURE

M.V.H. and F.A.K. report no conflicts of interests for this manuscript.

AUTHOR CONTRIBUTIONS

Menno V. Huisman drafted the manuscript. Frederikus A. Klok reviewed and adapted the manuscript.

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