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Thromboprophylaxis Strategies for Hospitalized Patients With COVID-19

To the Editor:

We read with interest the updated guidelines for thromboprophylaxis in patients with COVID-19 in this issue of CHEST.1 As stated in this and the previous version,2 the intent of these guidelines is to provide guidance regarding the optimal thromboprophylaxis strategies for VTE. However, although most of the recommendations align with the available evidence, it is our opinion that the first recommendation regarding the subgroup of moderately ill (noncritical) hospitalized patients does not. Although the risk ratio for VTE was 0.48 in favor of therapeutic anticoagulation (TA), additional meta-analyses of the risk difference for the same data show that, compared with prophylactic anticoagulation, TA was associated with a reduction of only 1.3% (95% CI, 0.6%-2.5%) in the risk of VTE with an associated increase in the risk of major bleeding of 0.9% (95% CI, 0.6%-1.7%). In addition, a meta-analysis of the reported main outcome for each of the four studies shows a risk ratio of 0.8 (95% CI, 0.5-1.2), suggesting no advantage of the intervention across all trials with the caveat that the main outcomes designed for all four studies were not the same. Therefore, the recommendation favoring TA was made on the basis of the reported advantage on organ support-free days for the multiplatform trial only, which amounted to only 4% (95% CI, 0.5%-7.2%).3 In our opinion, this deviates from the original intent of the guidelines, making their adoption confusing and potentially harmful.

In addition, the generalizability of the findings for the four trials is questionable as, overall, they included only 11% of more than 32,000 screened patients. In particular, the risk of bleeding is significant in these patients as shown by a systematic review and meta-analysis, including more than 18,000 hospitalized patients with COVID-19, reporting a pooled incidence of total and major bleeding of 7.8% and 3.9%, respectively, with the highest pooled incidence estimate among patients receiving intermediate- or full-dose anticoagulation (21.4%).4 In another cohort study of 1,965 patients receiving either intermediate or therapeutic anticoagulation, major bleeding events occurred in 5.7%.5 These figures differ from those reported in the four trials included in the guidelines, suggesting again a potential issue of generalizability.

We strongly believe that despite emerging data, TA strategies should not be considered standard of care yet, and if they are used outside of randomized trials, they must be executed very carefully on a case-by-case basis with multidisciplinary input and careful documentation.

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Response

To the Editor:

We agree with Porres-Aguilar and colleagues that therapeutic-dose anticoagulation should not be the standard of care for all noncritically ill, hospitalized patients with COVID-19 and, therefore, we provided several specifications to our recommendation in the recent update to the CHEST guideline and expert panel report.1 We specifically suggest that heparin be used, because its benefits do not appear to extend to other anticoagulants, and that therapeutic dosing be considered only in patients who are at low risk of bleeding.1,2

We also agree that the reduction in VTE may be offset by the increased risk of bleeding when using therapeutic-dose heparin in hospitalized patients with COVID-19. However, we disagree about the clinical importance of observed differences in organ support among the more recent randomized controlled trials (RCTs). One trial reported that therapeutic-dose heparin was associated with a 4% absolute increase in organ support-free days and a 4.5% absolute increase in survival without organ support in noncritically ill, hospitalized patients with COVID-19.3 We believe that these differences are clinically important, relevant to patients and physicians, and reduce resource use.

Some misinterpretation of data in the letter from Porres-Aguilar and colleagues also needs to be highlighted. Although the meta-analysis by Jiménez and colleagues4 included more than 18,000 patients, the risk of major bleeding was reported only in five of 47 studies (n = 1,411 patients). The risk of major bleeding ranged from 2.2% to 11.3% in the four retrospective studies and was 2.7% in the only prospective cohort study. Furthermore, the meta-analysis did not report major bleeding risk by disease severity. Because admission to the ICU is associated with an increased risk of bleeding, comparing bleeding risks of observational studies that included both critically and noncritically ill patients with bleeding risk in RCTs including only noncritically ill patients is not meaningful. Last, in the prospective cohort study, the risk of major bleeding while receiving intermediate- or therapeutic-dose anticoagulation was significantly lower in noncritically ill compared with critically ill patients [28 of 1,176 (2.4%) vs 84 of 789 (10.6%)].5 Interestingly, the estimate in noncritically ill patients is similar to the major bleeding risk observed in RCTs (range, 0.9%-2.4%).2,5,6,7

Overall, the risk of major bleeding in patients with COVID-19 who receive therapeutic-dose anticoagulation is underreported in observational studies but appears to be similar to the risks observed in RCTs. As detailed in the recent update of the CHEST guideline and expert panel report,1 it is critical to assess bleeding risk before the use of anticoagulation, and therapeutic-dose heparin should be considered only for noncritically ill, hospitalized patients with COVID-19 who have a low risk of bleeding. We would also like to highlight broader issues related to the potential benefits of therapeutic heparin that are discussed in a recent Point-Counterpoint editorial submitted by several of the guideline’s authors.8

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