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Age-adjusted D-dimer cutoffs to guide anticoagulation in COVID-19

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We read with great interest the Article by Renato D Lopes and colleagues[1] showing that, among patients hospitalised with COVID-19 and elevated D-dimer concentration, in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban to day 30 did not improve clinical outcomes but increased bleeding compared with prophylactic anticoagulation. However, in their analysis, the authors do not appear to have adequately considered the potential influence of the D-dimer concentration calculated with an age-adjusted cutoff.[2] According to current international guidelines,[3,4] an age-adjusted D-dimer test threshold must be considered for people older than 50 years, as in the case of this study, in which the mean age was 56·6 years (SD 14·3). Furthermore, considering that risk of mortality and severe forms of COVID-19 pneumonia increase with ageing,[5] it seems reasonable to prefer the adoption of an age-adjusted cutoff in this patient group. Therefore, the results of this large, multicentre, randomised trial should be interpreted cautiously for patients with COVID-19.

We declare no competing interests.

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1 Lopes RD, de Barros e Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet* 2021; **397:** 2253–63.

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Authors' reply

We appreciate the issues related to normal age-related D-dimer concentrations raised by Marco Zuin and colleagues. The ACTION study[1] is a randomised trial designed pragmatically to answer the question of whether patients hospitalised with COVID-19 and elevated D-dimer concentration, without another indication for anticoagulation, should routinely receive therapeutic anticoagulation with the factor Xa inhibitor, rivaroxaban. We found that rivaroxaban 20 mg once daily for 30 days had no benefit and significantly increased bleeding compared with in-hospital prophylactic heparin.

Early in the COVID-19 pandemic, observational data suggested that thrombotic events were high in patients with COVID-19 and even higher among patients with an elevated D-dimer concentration.[2] In light of the available information at the time, coupled with the fact that the D-dimer concentration of many patients with COVID-19 was measured when they were hospitalised, we included an elevated D-dimer concentration, defined as above the assay (not age-adjusted) upper limit of normal in each site, as an inclusion criterion for the ACTION trial. D-dimer concentrations are not routinely measured to guide therapeutic anticoagulation decision making in patients without COVID-19,[3] and the purpose of enrolling patients with an elevated D-dimer concentration in ACTION was to increase the trial population's risk of thrombotic events and not to establish D-dimer concentrations as a diagnostic tool to guide therapeutic anticoagulation in patients hospitalised with COVID-19.

A prespecified subgroup analysis of ACTION showed that the main results were consistent, irrespective of D-dimer concentrations.[1] Similar results have been shown in other randomised trials investigating anticoagulation in patients with COVID-19, in which D-dimer concentrations at presentation (elevated *vs* normal *vs* not collected) did not influence the main results.[4,5] Furthermore, when we used age-adjusted D-dimer upper limits of normal, as proposed by Zuin and colleagues, we found that most (>90%) patients over the age of 50 years still had an elevated age-adjusted D-dimer concentration at study entry. Not surprisingly, when we excluded the fewer than 10% of patients who did not have an elevated age-adjusted D-dimer concentration, our main results remained consistent with those in the overall population (win ratio 0·87 [95% CI 0·59–1·26]). Therefore, the results from the ACTION trial are relevant, robust, and provide high-quality evidence to avoid the routine use of therapeutic rivaroxaban—in the absence of another evidence-based indication for oral anticoagulation—in patients hospitalised with COVID-19, irrespective of D-dimer concentration.

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Department of Error

Shikino K, Sato R, Hanazawa N, Ikusaka M. Chronic clicking tinnitus due to palatal tremor: essential or secondary? Lancet *2021;* **397:** *e16*—In this Clinical Picture, Manato Yasuda has been added as an author. In the second sentence of the fifth paragraph, treatment dose has been corrected to 3 mg clonazepam orally per day. These corrections have been made to the online version as of Oct 7, 2021.