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therapies, were not used consistently in some studies, which raises concerns for external validity.

As a whole, the best evidence to date suggests that therapeutic anticoagulation likely benefits some patients who are moderately ill with COVID-19, but the concerns listed earlier urge us to avoid blindly following the guidelines and instead to consider carefully the risks and benefits for each individual patient.

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Rebuttal From Dr Tritschler et al
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We agree with the point made by Jimenez et al1 that consideration of bleeding risk is essential when evaluating administration of therapeutic anticoagulation. However, although well-intended, “first do not harm” is not an appropriate argument. If taken literally, anticoagulation could never be administered because it is well-known that anticoagulation increases the risk of bleeding. Instead, physicians must balance benefits with potential risks. Their assertion that therapeutic dose heparin should not be implemented for any patient because some patients that do not meet the eligibility criteria of randomized controlled trials (RCT) may not benefit is hard to follow. In fact, current clinical practice guideline recommendations on the use of therapeutic dose anticoagulation in different patient populations are based on RCTs that all used stringent eligibility criteria (Table 1).2 These eligibility criteria are

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### TABLE 1

Selected Recommendations From CHEST Guidelines and Expert Panel Reports and Selected Exclusion Criteria of the Randomized Controlled Trials That Were Considered for These Recommendations²,⁵

| CHEST recommendation                                                                 | Exclusion criteria of pertinent randomized controlled trials                                                                 | Exclusion criteria of pertinent randomized controlled trials                                                                 |
|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| In patients with VTE, we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over vitamin K agonist as treatment-phase anticoagulant therapy. | Active bleeding or high risk for bleeding                                                                                     | Contraindication to anticoagulation                                                                                           |
| In patients with acute VTE in the setting of cancer, we recommend an oral Xa inhibitor over low-molecular-weight heparin for the initiation and treatment phases of therapy. | Active bleeding or high risk for bleeding                                                                                     |                                                                                                                                |
| In patients with acute illness hospitalized with COVID-19 who have a low risk of bleeding, we suggest therapeutic dose heparin over current standard-dose anticoagulant thromboprophylaxis. | Contraindication to anticoagulation                                                                                           |                                                                                                                                |
| Anemia                                                                                 | Anemia                                                                                                                         | Anemia                                                                                                                         |
| Thrombocytopenia                                                                       | Thrombocytopenia                                                                                                               | Thrombocytopenia                                                                                                               |
| Uncontrolled hypertension                                                               | Uncontrolled hypertension                                                                                                     | Uncontrolled hypertension                                                                                                     |
| Recent major surgery                                                                   | Recent brain, spinal, or ophthalmic surgery                                                                                   | Recent major surgery                                                                                                          |
| Recent stroke                                                                          | Intracranial malignancy                                                                                                       | Recent stroke                                                                                                                 |
| Recent intracranial bleeding                                                            | Nonsteroidal antiinflammatory drug/antiplatelet drug other than acetylsalicylic acid ≤ 100 mg                              | History of intracranial bleeding                                                                                                |
| Recent intracranial surgery                                                             | Creatinine clearance < 30 mL/min                                                                                               | Recent intracranial surgery                                                                                                    |
| Intracranial neoplasm, cerebral aneurysm, or arteriovenous malformation                 | Acute hepatitis, chronic active hepatitis, liver cirrhosis, or alanine aminotransferase or aspartate aminotransferase > 3 times upper limit of normal | Intracranial malignancy, cerebral aneurysm, mass lesions of the CNS, or history of arteriovenous malformation                      |
| Nonsteroidal antiinflammatory drug/antiplatelet drug other than acetylsalicylic acid ≤ 100 mg | Total bilirubin > 2 times upper limit of normal                                                                              | Dual antiplatelet therapy                                                                                                      |
| Recent GI bleeding                                                                      | Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of VTE                 | Recent GI bleeding                                                                                                             |
| Active peptic ulcer                                                                    | Pregnancy or breastfeeding                                                                                                    | History of bleeding diatheses (eg, hemophilia)                                                                                  |
| Recent acute coronary syndrome                                                          | Eastern Cooperative Oncology Group performance status of 3 or 4                                                               | Thrombolysis within the previous 7 d                                                                                           |
| Creatinine clearance < 25-30 mL/min                                                     | Life expectancy < 6 mo                                                                                                         | Presence of an epidural or spinal catheter                                                                                     |
| Alanine aminotransferase or aspartate aminotransferase > 2 times upper limit of normal | Patient considered unsuitable for inclusion                                                                                   | Pregnancy                                                                                                                     |
| Total bilirubin > 1.5 times upper limit of normal                                       | ...                                                                                                                            | Imminent death                                                                                                               |
| Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of VTE | ...                                                                                                                            | ...                                                                                                                            |
| Pregnancy or breastfeeding                                                              | ...                                                                                                                            | ...                                                                                                                            |
| Life expectancy < 6 mo                                                                  | ...                                                                                                                            | ...                                                                                                                            |
| Patient considered unsuitable for inclusion                                             | ...                                                                                                                            | ...                                                                                                                            |
Similar for the use of therapeutic heparin in patients with acute illness who are hospitalized with COVID-19. RCTs provide the best experimental design to study interventions; it is common to select participants who may gain the greatest benefit from the intervention. RCTs aim to provide evidence for relative treatment effectiveness under optimal conditions. Such relative effects can often be applied to other populations, but physicians are required to estimate absolute risk differences that are based on relative benefits (or harms) and absolute baseline risks of an individual patient.3

Some of the alleged limitations of RCTs evaluating therapeutic dose heparin in patients with acute illness with COVID-19 need to be addressed.1 First, the fact that 20% of participants who were allocated to the therapeutic heparin arm in the multiplatform trial received less than therapeutic dose anticoagulation is not a reasonable concern. If anything, nonadherence to the study protocol would have diluted treatment effects and biased effect measures towards the null. The same is true for inclusion of participants up to 14 days after admission in the REMAP-CAP trial. Of note, only 13% of the acutely ill patient population of the multiplatform trial was enrolled in REMAP-CAP. Second, although potential interaction by co-treatment is a potential concern, Jimenez et al1 use this argument one-sided: What if therapeutic heparin diminishes the efficacy of other established treatments that were studied in patients who did not receive therapeutic heparin? The urgency to find effective treatments for a novel disease left investigators no choice but to study interventions simultaneously. Third, the assumptions that patients were kept on organ support because of the open-label trial design are unfounded, speculative, and unlikely, given the shortage of ICU beds during the pandemic. Furthermore, Jimenez et al1 criticize that none of the trials included VTE in the primary outcome, except for the HEP-COVID trial. Ascertainment bias of thrombotic events was the exact reason that trials did not include VTE in the primary outcome or, when they did, performed screening ultrasonography as in the HEP-COVID trial. Finally, requiring supplemental oxygen was not part of the definition of organ support in the multiplatform trial. Furthermore, and as outlined in our editorial,4 physicians can define the most relevant threshold of organ support-free days based on their individual preference because treatment effect measures of the multiplatform trial can be applied to any threshold of cumulative probabilities on the scale.

As for any treatment of COVID-19, uncertainties remain, given the rapid evolution of the pandemic, novel virus variants, and new preventive and therapeutic options. However, best current evidence from four RCTs support the use of therapeutic heparin in hospitalized patients with acute illness who are not at high risk of bleeding.

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Rebuttal From Dr David Jimenez et al

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We thank our colleagues for their thoughtful insights in describing the potential role of therapeutic heparin in patients with COVID-19 who are not critically ill.1

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