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THE BRASS TACKS: CONCISE REVIEWS OF PUBLISHED EVIDENCE

# Higher-dose versus standard-dose prophylactic anticoagulation in hospitalized patients with COVID-19

**Brit Long MD**[1] | **Michael Gottlieb MD**[2]

[1]Department of Emergency Medicine, Brooke Army Medical Center, Fort Sam Houston, Texas, USA

[2]Department of Emergency Medicine, Rush University Medical Center, Chicago, Illinois, USA

**Correspondence**
Brit Long, MD, 3841 Roger Brooke Dr, Fort Sam Houston, TX 78234 USA.
Email: brit.long@yahoo.com

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| NNT Color recommendation | Yellow (Unclear if benefits) |
|---|---|
| Summary Heading | Higher-dose anticoagulation did not improve survival and increased bleeding, but decreased venous thromboembolism |
| Benefits in NNT | No benefit in all-cause mortality<br>1 in 45 were helped (reduced venous thromboembolism) |
| Benefits in Percentages (absolute risk reduction) | No benefit in all-cause mortality, stroke, myocardial infarction, systemic arterial embolism<br>2.2% lower risk of venous thromboembolism |
| Harms in NNT (NNH) | 1 in 101 were harmed (increased risk of major bleeding)<br>1 in 18 were harmed (increased risk of any bleeding) |
| Harms in Percentages | 1% increased risk of major bleeding<br>5.3% increased risk of any bleeding |
| Efficacy Endpoints | All-cause mortality, venous thromboembolism, stroke, myocardial infarction, systemic arterial embolism |
| Harm Endpoints | Major bleeding, any bleeding |
| Who was in the studies | 7 trials of 5,145 hospitalized patients with COVID-19 |

**Editor's Note:** Brass Tacks are concise reviews of published evidence. This series is a result of collaboration between Academic Emergency Medicine and the evidence-based medicine website, "www.TheNNT.com." For inquiries please contact the section editor, Shahriar Zehtabchi, MD (email: shahriar.Zehtabchi@downstate.edu).

## NARRATIVE

Coronavirus disease 2019 (COVID-19) is a global pandemic, which has resulted in over 230 million cases and 4.7 million deaths as of September 25, 2021.[1,2] Literature suggests those with moderate or severe disease have increased endothelial activation and inflammation, coagulopathy, and elevated D-dimer levels, which may increase thromboembolic events.[2–4] Breakthrough thromboembolic events in hospitalized COVID-19 patients receiving preventive anticoagulation and observations of heparin resistance have raised the question of whether higher-dose anticoagulation may be beneficial.[5–7]

The systematic review summarized here included randomized controlled trials (RCTs) comparing higher-dose versus standard-dose preventive anticoagulation in hospitalized patients with COVID-19.[8] Authors included all types of anticoagulants. Dosing was defined by the individual trials. Authors pooled therapeutic and intermediate dosing regimens into the escalated-dose group. Primary outcomes included all-cause death at the longest follow-up available and major bleeding. Secondary outcomes included venous thromboembolism (VTE), myocardial infarction (MI), stroke, systemic arterial embolism, any bleeding, and minor bleeding.

The meta-analysis identified seven RCTs of 5,154 hospitalized patients with COVID-19.[8] Six RCTs used unfractionated heparin and low molecular weight heparin, with one study using rivaroxaban.[9] There were 1,893 critically ill patients and 3,261 non-critically ill patients, with follow up ranging from 14 to 90 days. Authors also performed a pre-planned subgroup analysis comparing critically ill and non-critically ill patients.

All-cause mortality did not differ between groups (17.8% versus 18.6%), but higher-dose anticoagulation increased major bleeding (2.4% vs 1.4%; risk ratio [RR] 1.7; 95% confidence interval [CI]:

  

1.2–2.6; absolute risk increase [ARI] 1%, number needed to harm [NNH] 101), and bleeding overall (RR: 2.0; 95% CI: 1.1–3.7; ARI 5.3%, NNH 18). Higher-dose anticoagulation was associated with less VTE (2.5% versus 4.7%; RR: 0.6; 95% CI: 0.4–0.7; absolute risk reduction 2.2%, number needed to treat [NNT] 45), but did not reduce MI, stroke, or arterial embolism. Results for subgroup analyses were consistent with overall results except for increased bleeding with higher-dose anticoagulation in non-critically ill patients that was not present in the critically ill patients.

## CAVEATS

COVID-19 is a complex disease, and patients at the beginning of the disease may be prothrombotic, while in later or more severe forms they can develop an increasing bleeding risk.[10] Thus, timing of anticoagulation may be crucial. It is possible at earlier stages of disease a higher dose of anticoagulation may be beneficial, while in later stages, this may be harmful. In the present meta-analysis, median time from symptom onset to randomization was approximately 10 days, suggesting future studies should assess the impact of timing.

There are several other important limitations. There was significant heterogeneity for all-cause death; major bleeding and VTE occurred more often in critically ill patients; and some subgroups were too small for useful analysis. Importantly, each trial included in this meta-analysis individually defined major bleeding, resulting in significant heterogeneity concerning this outcome. Duration of follow-up also varied, ranging from 14 days to 90 days. Only the ACTION trial used a direct-acting oral anticoagulant (DOAC) as anticoagulation,[9] limiting the ability to assess these agents. Moreover, there was heterogeneity in dosing with only two trials using an intermediate dose of anticoagulation rather than full dose.[11,12]

Based on the evidence, we have assigned a color recommendation of Yellow (Unclear if benefit) for higher-dose prophylactic anticoagulation compared to standard-dose in hospitalized patients with COVID-19. The lack of mortality benefit, increase in bleeding, and reduction in VTE suggest a complicated array of effects requiring larger, more rigorous trials and careful subgroup assessments. There are over 30 RCTs currently enrolling patients to evaluate the role of anticoagulation in patients with COVID-19, and we await further data assessing timing, specific patient populations (e.g., elderly, ventilated, pediatric), dosing, and agent.

### CONFLICTS OF INTEREST

None.

### ORCID

*Brit Long* https://orcid.org/0000-0003-4770-8869
*Michael Gottlieb* https://orcid.org/0000-0003-3276-8375

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