Full-dose blood thinners reduce need for organ support in moderately ill COVID patients

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A large clinical trial conducted worldwide shows that treating moderately ill hospitalized COVID-19 patients with a full-dose blood

thinner reduced their need for organ support, such as mechanical ventilation, and improved their chances of leaving the hospital. However, the use of this treatment strategy for critically ill COVID-19 patients requiring intensive care did not result in the same outcomes. The formal conclusions from the trial, which was supported in part by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, appear online in *The New England Journal of Medicine*.

"These results make for a compelling example of how important it is to stratify patients with different disease severity in clinical trials. What might help one subgroup of patients might be of no benefit, or even harmful, in another," said NHLBI Director Gary H. Gibbons, M.D.

Researchers have observed that in some people who died from COVID-19, blood clots had formed throughout their bodies, even in their smallest blood vessels. Antithrombotics, which include blood thinners or anticoagulants, help prevent clot formation in certain diseases. Doctors did not know which antithrombotic drug, what dose, and at what point during the course of COVID-19, antithrombotics might be effective. To answer these urgent questions, three international partners came together and harmonized their trial protocols to study the effects of using a full, or therapeutic dose, of the blood thinner heparin versus a low, or prophylactic dose, of heparin in moderately and critically ill patients hospitalized with COVID-19.

Researchers defined moderately ill patients as those hospitalized for COVID-19 without the requirement of organ support, and critically ill patients as those hospitalized for COVID-19 requiring intensive care level of support, including respiratory and/or cardiovascular organ support.

In April 2020, hospitalized COVID-19 patients received either a low or full dose of heparin for up to 14 days after enrollment. By December

2020, interim results indicated that full-dose anticoagulation did not reduce the need for organ support and may even cause harm in critically ill patients. However, one month later, interim results indicated that full doses of heparin likely benefited moderately ill patients.

"The formal conclusions from these studies suggest that initiating therapeutic anticoagulation is beneficial for moderately ill patients and once patients develop severe COVID-19, it may be too late for anticoagulation with heparin to alter the consequences of this disease," said Judith Hochman, M.D., senior associate dean for Clinical Sciences at New York University, a corresponding author of the moderately ill study and study chair of the NIH-funded trial partner Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 (ACTIV-4) Antithrombotics Inpatient. "The medication evaluated in these trials is familiar to doctors around the world and is widely accessible, making the findings highly applicable to moderately ill COVID-19 patients."

The final analysis of trial data included 1,074 critically ill and 2,219 moderately ill patients. For both moderately and critically ill patients, researchers looked at how long they were free of organ support up to 21 days after enrollment. Among moderately ill patients, researchers found that the likelihood of full-dose heparin to reduce the need for organ support compared to those who received low-dose heparin was 99%. A small number of patients experienced major bleeding, though this happened infrequently. For critically ill patients, full-dose heparin also decreased the number of major thrombotic events, but it did not reduce the need for organ support or increase their chances of leaving the hospital early after receiving treatment.

The participating trials include: Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) Therapeutic Anticoagulation; Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC); and ACTIV-4

Antithrombotics Inpatient. In the United States, ACTIV-4 Antithrombotics Inpatient is being led by a collaborative effort with several universities, including the University of Pittsburgh, a trial coordinating center, and New York University, the study chairs' office and a coordinating center. ACTIV-4 Antithrombotics Inpatient is also conducting another study to test the effects of adding an anti-platelet agent to anticoagulation.

"More work needs to be done to continue to improve outcomes in patients with COVID-19," said Matthew D. Neal, M.D., the Roberta G. Simmons Associate Professor of Surgery at the University of Pittsburgh, co-author of the moderately ill study and co-chair of ACTIV-4 Antithrombotics Inpatient. "Given what we know about the type of blood clots in patients with COVID-19, testing anti-platelet agents is a particularly exciting approach."

More information: Therapeutic Anticoagulation in Critically Ill Patients with Covid-19 – Preliminary Report, *New England Journal of Medicine* (2021). DOI: 10.1056/NEJMoa2105911

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