# Therapeutic Anticoagulation with Heparin in Patients with Covid-19

**TO THE EDITOR:** We read with interest the recent *Journal* articles (Aug. 26 issue)[1,2] about therapeutic anticoagulation in patients with Covid-19. We applaud the investigators for performing rigorous trials to address this important clinical concern in Covid-19. Remarkably, these studies show that the therapeutic benefit of anticoagulation is not from prevention of acute pulmonary embolism. The incidences of prospectively diagnosed acute pulmonary embolism among patients who were hospitalized for Covid-19 were relatively low: 1.3% (29 of 2226) among noncritically ill patients and 5.1% (55 of 1089) among the critically ill. These incidences were similar to those observed in other prospective trials involving patients with Covid-19.[3]

Early retrospective reports suggested alarmingly high incidences of pulmonary embolism among patients who were hospitalized for Covid-19. However, those studies preferentially included patients who had already received contrast-enhanced computed tomographic pulmonary angiography for clinical reasons, including the suspicion for acute pulmonary embolism.[4] If such studies were excluded, a meta-analysis of studies involving patients who were hospitalized for Covid-19 showed incidences of acute pulmonary embolism that were similar to those among similarly ill patients without Covid-19.[5] The recently published trials confirmed that acute pulmonary embolism is not as frequent among patients with Covid-19 as previously assumed.

Timothy M. Fernandes, M.D., M.P.H.
W. Cameron McGuire, M.D., M.P.H.
Timothy A. Morris, M.D.

University of California, San Diego, School of Medicine
La Jolla, CA
tfernandes@health.ucsd.edu

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1. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med 2021;385:777-89.
2. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 2021;385:790-802.
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 2020;383:1813-26.
4. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Res Pract Thromb Haemost 2020;4:1178-91.
5. Gallastegui N, Zhou JY, Drygalski AV, Barnes RFW, Fernandes TM, Morris TA. Pulmonary embolism does not have an unusually high incidence among hospitalized COVID19 patients. Clin Appl Thromb Hemost 2021;27:1076029621996471.

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**TO THE EDITOR:** Contrasting results have been reported about the preferred anticoagulation therapy in patients with SARS-CoV-2 infection. The two recent articles published in the *Journal* might contribute to understanding the reasons for these contrasts. The main findings were that therapeutic-dose heparin or low-molecular-weight heparin reduced mortality among patients with moderate infection but not among those with severe infection.[1]

A possible explanation for this difference is that SARS-CoV-2 infection, once it reaches a severe state, may become an irreversible condition. The similarities between the hematologic changes associated with severe SARS-CoV-2 infection and diffuse intravascular coagulation support the hypothesis that SARS-CoV-2 infection may lead initially to functional changes of the endothelial barrier that with time may become irreversible organic changes. Even if not specified in the two articles, we may assume that patients with severe illness came to that situation after a longer infection period.

Thus, we emphasize the importance of an aggressive therapeutic approach for all patients who are hospitalized for Covid-19. This aggressive approach should include all therapeutic tools to address a disease that in its more severe forms is the result of multiple factors.

Antonio V. Sterpetti, M.D.
Sapienza University
Rome, Italy
antonio.sterpetti@uniroma1.it

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1. Ten Cate H. Surviving Covid-19 with heparin? N Engl J Med 2021;385:845-6.

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**THE AUTHORS REPLY:** In our multiplatform, randomized, controlled trial involving patients hospitalized for Covid-19, therapeutic-dose anticoagulation with heparin was found to be beneficial in noncritically ill patients but not in critically ill patients. In noncritically ill patients, therapeutic-dose anticoagulation with heparin increased organ support–free days, an ordinal outcome combining hospital survival and receipt of intensive care unit–level organ support.

To individualize benefit and balance risk, identifying factors that may contribute to heterogeneous treatment effects is important and is currently being evaluated by our team in secondary analyses. We agree with Sterpetti that once a patient becomes critically ill, the clinical course may be too advanced to be beneficially influenced by heparin. What defines such a state, however, is unknown and may relate to the clinical time course, spectrum of coagulation activation, host response, or the integration of several known or yet-to-be recognized factors. Baseline D-dimer levels did not appear to discriminate relative therapeutic benefit on the basis of the D-dimer cutoff used, although absolute benefit was more apparent among those with elevated D-dimer levels given higher event frequencies.

Fernandes et al. are correct to highlight that the benefit of therapeutic-dose heparin in noncritically ill patients was not fully attributable to a reduced occurrence of pulmonary embolism and that incidences of venous thromboembolism (VTE) that were reported early in the pandemic were higher than those currently observed. This may relate to confounding by indication in observational studies that may include patients who had already received a diagnosis of VTE and been treated for it,[1] as well as the use of active screening in some studies. Randomized trials of therapeutic-dose heparin involving patients with Covid-19 were also completed after glucocorticoids had been introduced as standard care and on a background of increasing use of interleukin-6 receptor antagonist — both factors that may reduce VTE occurrence. In an evolving pandemic that includes changes in circulating variants, standards of care, and the at-risk population, the true incidence of VTE due to Covid-19 is uncertain and worthy of continuing study. The reduced use of organ support may imply that heparin may also have beneficial effects on microvascular thrombosis, antiinflammatory effects, and possibly antiviral effects,[2] all of which mitigate organ damage.

Ryan Zarychanski, M.D.

University of Manitoba
Winnipeg, MB, Canada
ryan.zarychanski@umanitoba.ca

Patrick R. Lawler, M.D., M.P.H.

Peter Munk Cardiac Centre
Toronto, ON, Canada

Ewan Goligher, M.D., Ph.D.

University of Toronto
Toronto, ON, Canada

Since publication of their article, the authors report no further potential conflict of interest.

1. Psaty BM, Koepsell TD, Lin D, et al. Assessment and control for confounding by indication in observational studies. J Am Geriatr Soc 1999;47:749-54.
2. Clausen TM, Sandoval DR, Spliid CB, et al. SARS-CoV-2 infection depends on cellular heparan sulfate and ACE2. Cell 2020;183(4):1043-1057.e15.

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## Long-Term Complications in Youth-Onset Type 2 Diabetes

**TO THE EDITOR:** The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study Group (July 29 issue)[1] reported complications over 15 years of follow-up in a large sample of participants who had onset of type 2 diabetes in youth. We believe that bariatric surgery deserves stronger endorsement in patients with youth-onset type 2 diabetes, given its metabolic effects.

Long-term data from randomized, controlled trials have shown that bariatric surgery has promising outcomes in patients with type 2 dia-