THE AUTHORS REPLY: We confirm that we did use the Fine–Gray version of the Cox regression model in the analysis of the requirement for long-term oxygen therapy, for which death was an obvious competing event.[1] The hazard ratio and confidence interval for the long-term oxygen therapy outcome were therefore derived from the parameter estimates of the Fine–Gray competing-risk model. We believe that the confusion arose from a lack of correspondence between the statistical analysis described in our article and the statistical analysis plan in the trial protocol (available with the full text of our article at NEJM.org).

Prespecified subgroup analyses were limited to the effect of nocturnal oxygen at various thresholds of mean nocturnal saturation. We did not proceed with this analysis, because clinically meaningful subgroups could not be defined. However, we did examine the effect of nocturnal oxygen on quality of life with the use of the St. George's Respiratory Questionnaire. We found no evidence of an effect of nocturnal oxygen on any of its domains. The mechanisms by which supplemental oxygen affects COPD progression are poorly understood. At best, the measurement of inflammatory cytokines would have represented an intermediate outcome.

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

1. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.

DOI: 10.1056/NEJMc2032006

Tocilizumab in Covid-19

TO THE EDITOR: Stone et al. (Dec. 10 issue)[1] report that tocilizumab had no significant effect on the risk of intubation or death in moderately ill patients hospitalized with coronavirus disease 2019 (Covid-19). These results should not be extrapolated to other populations of patients with Covid-19, particularly the critically ill. Our multicenter cohort study involving 3924 critically ill patients with Covid-19 showed that early administration of tocilizumab was associated with prolonged survival.[2] The patients enrolled in our study were fundamentally different from those in the trial by Stone et al. (Fig. 1), which may account for the divergent findings.

The trial by Stone et al. was also severely underpowered. In the placebo group, the percentage of patients with a primary outcome event (i.e., intubation or death) was 12.5%, far lower than the anticipated 30%. A post hoc power calculation reveals that with this event rate and the number of patients enrolled (243), it would have been nearly impossible for the trial to have shown a significant effect: the risk of the primary outcome would have had to have been

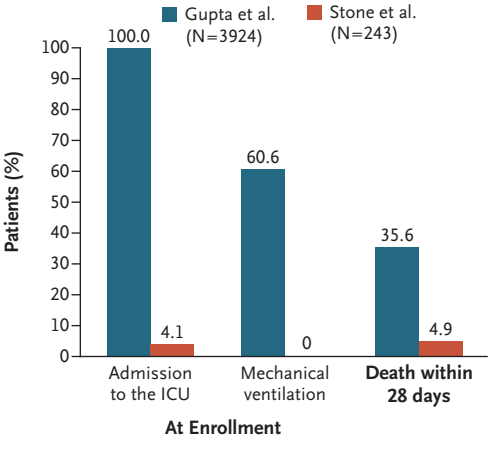

Figure 1. Severity of Illness at Admission and 28-Day Mortality.

Shown are the percentages of patients who were admitted to the intensive care unit (ICU) or were receiving mechanical ventilation at the time of enrollment and the percentages of patients who died within 28 days after enrollment in the trial by Stone et al.[1] and the study by Gupta et al.[2]

more than 80% lower with tocilizumab than with placebo. Therefore, the trial results cannot be interpreted as being definitively null, since the imprecise estimates are also compatible with either benefit or harm.

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No potential conflict of interest relevant to this letter was reported.

This letter was published on December 22, 2020, at NEJM.org.

1. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020;383:2333-44.
2. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med 2020 October 20 (Epub ahead of print).

DOI: 10.1056/NEJMc2032911

THE AUTHORS REPLY: Leaf and colleagues observe that our results should not be extrapolated to other populations of patients with Covid-19. We reported that tocilizumab had no significant effect on any of multiple efficacy measures evaluated in moderately ill patients hospitalized with Covid-19, including the primary outcome of intubation or death. These conclusions were supported by multivariate analyses that controlled for baseline serum interleukin-6 concentrations and other factors believed to influence Covid-19 outcomes. Our trial was not powered to detect small effects because of the lower-than-expected percentage of patients in the placebo group who had a primary outcome event. Nevertheless, our conclusions are valid because the results suggest that tocilizumab had essentially no effect in our trial population: the Kaplan–Meier curves for the tocilizumab and placebo groups were almost completely overlapping, and the hazard ratio estimates were near 1. Moreover, we were careful to conclude that because of the wide confidence intervals in our analyses, some benefit (or harm) from tocilizumab administration could not be ruled out by our results.

Leaf and colleagues refer to their cohort study involving critically ill patients with Covid-19.[1] That study concluded that early treatment with tocilizumab might reduce mortality. The authors conceded that their findings might be susceptible to unmeasured confounding and indicated that "further research from randomized clinical trials is needed." We note that randomized, double-blind, placebo-controlled trials involving critically ill patients with Covid-19 have been reported.[2,3] Those trials, like ours, reported negative results.

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Dr. Stone reports having received grant support from Bristol Myers Squibb and consulting fees from Novartis, Q32Bio, Spruce Biosciences, and Viela Bio. An updated disclosure form is available with the full text of his article at NEJM.org. Since publication of his article, Dr. Stone reports having received consulting fees from Argenx. No further potential conflict of interest relevant to this letter was reported.

This letter was published on December 22, 2020, at NEJM.org.

1. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med 2020 October 20 (Epub ahead of print).
2. Park B. US trial investigating sarilumab for COVID-19 stopped. MPR, July 7, 2020 (https://www.empr.com/home/news/drugs-in-the-pipeline/sarilumab-interleukin-6-antagonist-covid19-mechanical-ventilation/).
3. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. July 29, 2020 (https://www.roche.com/investors/updates/inv-update-2020-07-29.htm).

DOI: 10.1056/NEJMc2032911