TO THE EDITOR: I read with interest Doumouras and colleagues’ article (1) reporting decreased mortality in patients after bariatric surgery. Using a robust database, the authors also conducted several subgroup analyses to evaluate the association between bariatric surgery and death from different causes to strengthen their results. They stated that bariatric surgery was associated with lower all-cause, cardiovascular, and cancer mortality. However, I am concerned that their interpretation of the results for decreased cancer mortality may be misleading.

According to Figure 2, panel C, and Supplement Table 2 of their article, the adjusted hazard ratio for subsequent cancer death in patients who had bariatric surgery was 0.54 (95% CI, 0.36 to 0.80). This implies that, compared with patients in the nonsurgical group, mortality was reduced by 46%. Yet, in the fifth paragraph of the Results section, the authors stated that bariatric surgery was associated with a 56% reduction in cancer mortality, which differs from the results previously provided. Furthermore, the first paragraph of the Discussion section states that lower associations with observed cardiovascular mortality and cancer mortality were 63%; however, decreased mortality of 63% was not previously mentioned among the results related to cancer death in this article. According to Supplement Table 2, this value should be 46%.

The information about cancer mortality in this article may be misleading, and I am uncertain whether the values provided in the text or Supplement Table 2 are correct.

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How to Quantify and Interpret Treatment Effects in Comparative Clinical Studies of COVID-19

TO THE EDITOR: McCaw and colleagues (1) raised issues about recovery in the presence of the competing risk for death in the context of COVID-19 trials. We contend that our setting slightly differs from the typical competing risk setting. A typical competing risk scenario might involve time to coronary heart disease death, with the patient dying of stroke. Having a stroke is undoubtedly informative about what that patient’s time to coronary heart disease death would have been, but we cannot reliably impute the time to coronary heart disease death. In the COVID-19 setting, the patient is dying of COVID-19 itself. Death gives complete information about time to recovery; it is infinite. We therefore respectfully disagree with McCaw and colleagues’ statement, “In fact, the recovery times of patients who have died could not be defined or estimated.” Survival software does not allow infinite times to recovery, but imputing any time longer than the longest possible follow-up (28 days in the ACTT-1 [Adaptive COVID-19 Treatment Trial]) fortunately gives the same answer. We also disagree with the statement, “The strategy adopted by ACTT-1 investigators for managing death as a competing risk is unusual.” In fact, it is common in clinical trials to assign the worst possible outcome to a patient who dies of the disease under study. In addition, with complete follow-up, our approach corresponds to the widely used Fine-Gray method for competing risks and our Kaplan-Meier curve corresponds to the cumulative incidence curve.

We acknowledge that our method poses an issue at an interim analysis. A patient enrolled 15 days ago who dies on...
study day 7 has an imputed 29 days of follow-up. The cumulative incidence and Fine–Gray approaches censor such a patient according to the eligible follow-up window, which for this patient would be 15 days. In the interim report of ACTT-1, the 2 approaches gave virtually identical answers; yet, we acknowledge that the Fine–Gray and cumulative incidence approaches are theoretically superior for interim analyses.

We all agree on certain statements, such as, “Moreover, because the potential death and recovery times of each patient are probably correlated, standard survival analysis methods that treat death as independent of censoring are not appropriate.” A standard survival analysis would censor recovery time at the time of death, which makes no sense when censoring is informative. The Kaplan–Meier method does make sense when imputing a recovery time that exceeds the longest possible follow-up. We also appreciate the interpretation of a restricted recovery time as a useful perspective. However, we believe that the Kaplan–Meier method in conjunction with imputation of the longest recovery time is also useful.

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TO THE EDITOR: We applaud McCaw and colleagues (1) for using the “well-established yet underused” method of accounting for competing risks in their time-to-recovery analyses of patients with COVID-19. Although their approach is valid, we recommend that they consider expanding their analysis to the established (and also underused) method of multistate modeling for time-to-event analyses (2). This method avoids several common survival biases (including those mentioned in their article) and gives deep insights into the time-dynamic progress of oxygen support and clinical outcomes in patients with COVID-19 (3).

Multistate models represent processes where a patient can occupy one of several states (such as levels of oxygen support) at a given time. This method has been shown on 2 real data sets of patients with COVID-19 that were extracted from published works in the New England Journal of Medicine (4, 5). This approach has several advantages. Unlike a competing risks model, where a patient moves permanently into one of several final states, multistate models allow repeated transitions (such as noninvasive ventilation → invasive ventilation) and thus model patients who may clinically improve and then subsequently decline (or vice versa).

Similar to the mean time in recovery displayed in Figure 3, panels B and C, of McCaw and colleagues’ article, average duration in specific oxygen support states can be calculated, thus informing decision makers on the health care needs of specific groups of patients. Furthermore, the cumulative incidence curves of various states can be consolidated into a single stacked probability plot. Doing so not only correctly acknowledges active cases by taking into account censoring but also shows how the duration of oxygen support is determined by the competing end points of death and discharge. These plots can show the predicted clinical course of an entire cohort of patients with COVID-19, as well as enable the comparison of patients with differing baseline characteristics. Of note, the graphs can directly show how both clinical end points and end points influencing hospital capacities differ between treatment groups in randomized clinical trials (6).

A picture is a thousand words, and it is unfortunate that we cannot include an example plot in this comment. However, researchers can conduct the analyses themselves with code in the statistical software R (R Foundation), example data sets, and plots that are publicly available in our article (3). We agree with the authors that “no single summary measure can capture all the information provided by the cumulative recovery curves.” However, we believe that the easy-to-interpret yet comprehensive information provided by a stacked probability plot is a step in the right direction.

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IN RESPONSE: As Dr. Proschan and colleagues state, in the presence of a competing risk, technically one must assign an arbitrarily large value to the time to recovery for a patient who died before recovery during the 28 days of follow-up (that is, treating death as the worst outcome). However, summarizing
the distribution of such an “improper” random variable is challenging. For example, the average recovery time would not be clinically meaningful. In addition, in the presence of censored observations, the procedure used in ACTT-1 can be problematic, as discussed in our article. For the interim data, because the censoring proportion and mortality rate for the study were not large, the reported results from ACTT-1 did not markedly differ from those obtained through the conventional competing risks procedure. On the other hand, for future studies with potentially longer follow-up, the censoring rate can be high, especially at the interim analysis.

Using the cumulative incidence curve under the competing risk setting to analyze data is more appropriate. To summarize the treatment effect with the time to recovery as the end point, a pseudo hazard ratio similar to that suggested by Fine and Gray (1) was used in ACTT-1. This ratio by itself is difficult to interpret clinically for quantifying the treatment effect. A simple, intuitive summary suggested in our article can be a viable alternative.

To explore the temporal profile of the treatment effect, using a graphical method to display the multinomial cell probabilities over time as suggested by Dr. Hazard and associates would certainly be informative. They would help to understand how the disease burden and progression change dynamically. Summary measures, such as the average duration spent in each state, can be obtained from the corresponding areas between the curves in the plot. Although there are no single overall summaries that can capture the entire profile across various stages, having a summary measure for decision making on the choice of treatments is important. For example, one may use a weighted average of those durations, provided it is clinically interpretable. The area under the cumulative incidence curve for the time to recovery in the presence of a competing risk as discussed in our article is also one such summary measure.

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IN RESPONSE: We thank Dr. Mathieson and colleagues for their comment. Guidelines are “guides” only and may not apply to all patients and clinical situations (1, 2). Thus, clinical guidelines are not intended to override clinicians’ judgments. We disagree with Dr. Mathieson and colleagues and believe that the interventions can be compared across the clinical indications. The effect of the interventions on outcomes is comparable across musculoskeletal injuries. The biology of the experience of pain in such conditions is similar; therefore, we can expect similar effects of interventions directed at pain relief. When provided with the list of patient-reported pain locations represented among trials included in the evidence review, our technical expert panel believed that patients would respond similarly to interventions.

Moreover, 48% of the 207 trials eligible for the NMA (including 4 of the 7 that enrolled patients with fracture) enrolled populations with mixed musculoskeletal injuries and reported aggregate results, indicating that trialists anticipated similar responses across different injuries. Statistical assessment provided additional confirmation: Between-study variance within closed loops of interventions and networks showed no evidence of incoherence (see Supplement Figures 3, 5, 7, 9, 11, 13, 15, and 17 in the accompanying systematic review and meta-analysis [2]).

We acknowledge in our guideline that, because of considerable heterogeneity in the presentation of acute pain, topical nonsteroidal anti-inflammatory drugs are not always appropriate first-line therapy (such as in cases of severe injury). We suggest several potential treatment options and highlight the importance of assessing individual patient-level risk factors and preferences.

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Why N95 Should Be the Standard for All COVID-19 Inpatient Care

TO THE EDITOR: I read Dau and colleagues’ commentary (1) with interest. Many of us are wrestling with the issue of what personal protective equipment should be used in the management of patients with COVID-19. It is a difficult decision that requires navigating current personal protective equipment shortages and evaluating how much weight to give prior studies on SARS-CoV-2 or influenza, among other challenges.

This difficult task is not made easier when viewpoints in such major journals as Annals state, “A 2016 meta-analysis evaluating the effectiveness of N95 respirators versus surgical masks in a health care setting found an odds ratio of 0.51 (95% CI, 0.19 to 1.41) for influenza-like illness. . . . This odds ratio shows the effectiveness of N95 respirators for reducing influenza-like illness and a compelling magnitude of protection against respiratory disease transmission with N95 respirators.”

An odds ratio confidence interval that crosses 1 (and not just by a small amount) does not show the effectiveness of N95 respirators; instead, it tells us that there is a great deal of uncertainty around the effect, including that the effect may be harmful. Trial data—including those by Radonovich and associates

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(2), which Dau and colleagues cite—show no superiority of N95 respirators versus surgical masks. Early literature coming out of the COVID-19 experience similarly has yet to show an advantage to N95 respirator use outside of aerosol-generating procedures. Universal N95 respirator use may prove to be superior; however, there is the potential for harm. For example, proper and consistent use of an N95 respirator is not easy. Furthermore, if supplies mandate extended use or reprocessing, risks are increased.

Science needs to drive our use of personal protective equipment. Claiming that a meta-analysis shows “the effectiveness of” and a “compelling magnitude of protection . . . with” N95 respirator use when the actual data state that the evidence is mixed and do not show either type of device to be clearly superior is misleading.

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TO THE EDITOR: Dau and colleagues’ commentary (1) makes the important point that recommendations for respiratory protection of health care workers exposed to SARS-CoV-2 have often fallen short. The recommendation that surgical masks are adequate outside the setting of procedures believed to generate aerosols is described as “merely a preference or a recommendation based on availability [of N95 respirators].” As noted, the superiority of N95 respirators in protecting against respiratory pathogens is supported by available literature and the performance characteristics of N95 respirators compared with that of surgical masks, given that SARS-CoV-2 seems to be transmissible by aerosols.

I am writing this comment not to dispute Dau and colleagues’ conclusions but to point out further implications. The current recommendation for the public to wear cloth masks is also based on availability. The problem lies not with the recommendation itself but with the rationale. Given health care workers’ consistently intense exposure, they should have first priority for use of respirators that actually protect the wearer. However, respirator shortage—not lack of rationale—should be cited as the reason not to recommend N95 respirator use for the general public.

If N95 respirators are more effective when worn in the health care setting, why would they not be more effective in other settings where the exposure can sometimes be just as intense? Why would they not be more effective for packing plant employees, extended-care workers, barbers, prison guards, prisoners, and many others? Given the variety of respirators used and the large number of wearers, many hospitals have used self-fit testing; as such, the fit test seems to be less of a barrier than once believed. Difficulties with the proper use of N95 respirators exist, but people are educable. Although the risk for contracting COVID-19 is lower for most non-health care workers, wider use of N95 respirators could make a big difference in the aggregate. In addition, I am sad to say, masks that protect the self as well as others might gain better acceptance in U.S. culture.

At the very least, public health authorities should protect their eroding credibility by forthrightly stating that cloth masks are recommended only because of an N95 respirator shortage. As stated in Dau and colleagues’ commentary, “Recognizing that . . . masks are substandard will empower our society to allocate resources to ensure the availability of N95 respirators.”

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IN RESPONSE: We agree with Dr. Drekonja that the example provided focused on the point estimate and did not emphasize the uncertainty based on the wide CI. We would like to provide additional data to support our view. The meta-analysis by Bartoszko and colleagues (1) showed an odds ratio of 1.31 (95% CI, 0.95 to 1.85) for influenza-like illness and 1.49 (CI, 0.98 to 2.28) for clinical respiratory illness, both favoring N95 respirators. The meta-analysis by Long and associates (2) for laboratory-confirmed respiratory viral infection—without including data from Radonovich and coworkers’ 2019 outpatient study (3) and Loeb and colleagues’ 2009 targeted-use trial (4)—showed a risk ratio of 0.58 (CI, 0.43 to 0.78), also favoring N95 respirators. We thank Dr. Drekonja for giving us an opportunity to provide this clarification.

Dr. Wilson emphasized the potential benefits of N95 respirators in various settings where prolonged exposure to SARS-CoV-2 may be expected. The World Health Organization (5) clarified that “short-range aerosol transmission, particularly in specific indoor locations, such as crowded and inadequately ventilated spaces over a prolonged period of time with infected persons cannot be ruled out.” As production of N95 respirators ramps up, there would be tremendous value to performing the cluster randomized controlled trials of N95 respirators versus medical masks in the community settings that Dr. Wilson described. As for fit, a study did find that “fit testing did not improve the efficacy of N95 respirators” (6). However, this study had a small sample size, and its findings may not be extrapolated to other N95 respirators.

Again, we strongly urge countries to allocate resources to ensure that personal protective equipment is easily available.
Doing so will eliminate the difficulty of making appropriate recommendations for this equipment based on availability and resources. Until then, universal face mask use has been shown to reduce the spread of disease within the community setting (7). We also hope for wider acceptance of mask use during a pandemic.

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