thrombectomy alone group were men vs 70% in the combined intravenous thrombolysis and mechanical thrombectomy group. Although imbalances between groups can occur by chance in a randomized clinical trial, it is unusual to have imbalances for several baseline variables simultaneously, particularly for important prognosis factors in patients with stroke, such as blood pressure, stroke severity, and stroke location. Therefore, we are concerned about systematic bias from the randomization process in this open-label trial.

Second, although the discrepancy between the primary outcome selection in the initial and final protocols was explained in the publication, the study hypothesis was not clearly stated in the protocol and did not follow the SPIRIT guidance. Additionally, the sample size description in both the final protocol and statistical analysis plan indicated that 178 patients were required, assuming a favorable outcome in 48.6% with mechanical thrombectomy alone and 35.2% with combined intravenous thrombolysis and mechanical thrombectomy. The noninferiority margin for the primary outcome was not predefined or considered in the sample size calculation for this “noninferiority” trial but was compared against an odds ratio of 0.74, derived from a previous meta-analysis. Also, the noninferiority margin was not clearly prespecified but was tested for the secondary outcome of modified Rankin Scale score reduction. In addition, the percentage of patients projected to drop out of this study decreased from 33% in the initial study design to 11% in the final study design. Because of these concerns, we believe further clarifications and justifications are needed to avoid misinterpreting the findings of this trial.

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In Reply

Dr Mai and colleagues describe some concerns with the SKIP study, including the balance of baseline characteristics between the 2 groups, the sample size, and the noninferiority margin for the secondary outcome.

First, patients in our study were randomized to 2 groups using a stratified permuted-block method for each hospital. Although an imbalance did exist between men and women in the study groups, other baseline characteristics, including blood pressure, stroke severity, and stroke location, were not statistically different between the 2 groups. We believe the male/female imbalance was due to chance alone. The odds ratio of noninferiority for the primary outcome was 1.09 (97.5% CI, 0.63 to ∞). In a post hoc analysis, the odds ratio adjusted for male/female sex was 1.11 (97.5% CI, 0.63 to ∞).

Second, in our initial study protocol, we projected a dropout rate of approximately 30% and therefore set the sample size at 200 to include 134 patients continuing the trial and 66 dropouts. At the time we applied to the institutional review board to change the primary outcome from superiority of poor outcome rate to noninferiority of favorable outcome rate, our study had enrolled 50 patients and had no dropouts. Therefore, the final protocol set the sample size at 200 to include 178 patients retained in the study and 22 dropouts.

Third, as pointed out by Mai and colleagues, we incorrectly used a noninferiority margin of 0.74 for the secondary outcome. The correct noninferiority margin, calculated as 0.78 from the result of the HERMES collaboration, does not change our results because the lower 97.5% CI of the odds ratio still passes across this margin (0.60 vs 0.78).

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CORRECTION

Incorrect Figure Data: In the Original Investigation titled “Association of First Primary Cancer With Risk of Subsequent Primary Cancer Among Survivors of Adult-Onset Cancers in the United States,” published in the December 22/29, 2020, issue of JAMA, incorrect data were shown in several figures. In Figure 1B and also in Figure 3B, the cell indicating “larynx” as the first primary cancer and “stomach” as the subsequent primary cancer should have been blank. In Figure 2A and Figure 2B, the subsequent primary cancer label indicating “urinary bladder” should be labeled as “vulva and other genital organs,” and the subsequent primary cancer label indicating “vulva and other genital organs” should be labeled as “urinary bladder.” This article was corrected online.