REPLY:

We thank Johansson and Salzer for their response to our article. We agree that several considerations of our study are limited by the small sample size. However, the main objection of the authors is with the statement in the conclusion of our article, "Overall, this report supports the selection of patients for intra-arterial therapy on the basis of favorable patient characteristics (small core, good collateral circulation) and low likelihood of recanalization with intravenous thrombolysis (large and proximal clot burden)." They fail to mention the sentence that follows, "Additional studies will be needed to further understand the continued benefit of intra-arterial treatment for patients with larger infarct burden or distal occlusions."

Any clinical trial is powered primarily to understand main effects. This was the case even with the Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial.[1] Subgroup analysis is to look for patterns that might help physicians make more considered assessments on prognosis and effect modification. These analyses are therefore not level 1 evidence but suggest the need for confirmatory studies within those subgroups. Some of these studies may be possible while others may never happen. Physicians then draw reasonable conclusions based on the data presented, their own heuristics, and any other current evidence to inform their practice. They can decide to wait for further confirmatory studies. This is what we suggested.

We agree that the absence of statistically significant effect modification by a variable on the relationship between the treatment and the outcome is not evidence for lack of effect modification. Small sample size is a problem with tests of effect modification in any clinical trial because the trial is invariably not powered to test for the presence or absence of such effect modification. We also agree that multiple testing within multiple subgroups increases the likelihood of type I error (stating that there is signal when there is none). Given the small sample size in our study, we therefore deliberately avoided looking for statistical interaction (effect modification) to avoid both problems described above. Observations of our results graphically (see Figs 1 and 4 in our article) suggest that there is evidence of benefit from intra-arterial therapy versus controls in patients with a small baseline infarct core and good collateral circulation; however, we wanted to caution our readers that they should not assume from our data that a similar effect exists in patients with a large baseline core or poor collaterals. This is so because biologically, it is plausible that these patients with large baseline infarcts or very poor collaterals may have poorer outcomes on average even with good treatment. Therefore, we suggested a cautionary last sentence, "Additional studies will be needed to further understand the continued benefit of intra-arterial treatment for patients with larger infarct burden or distal occlusions," instead of giving the readers a spurious message that patients with low ASPECTS or poor collaterals are likely to benefit to the same extent as patients with small core or good collaterals.

We therefore agree with the authors that future clinical trials and analysis of larger pooled datasets will be helpful in building more evidence for refining selection of patients who may benefit from intra-arterial therapy.[2] Our study is one small step in that direction.

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