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### *Reply:*

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## REPLY:

Thanks to Dr. Capocci and colleagues for their interest in our manuscript. Their comments appear to address: 1) the appropriateness of the manuscript for submission; 2) our departure from a rigid anatomic classification system; and 3) an additional “new” classification of their own.

No strangers to confusion and controversy requiring caution regarding the communication of historical classification constructs,<sup>1</sup> we came to our conclusions after we saw stroke angiograms in studies over 20 years, and ultimately, we were ourselves confused about the best way to analyze and report what we observed.

Regarding the appropriateness, we would have been remiss had we not looked beyond the original published results of the largest randomized interventional stroke treatment study to date with a focus on interventional subgroups.<sup>2</sup> Various issues raised in post hoc analysis should be of value to future investigators planning their own studies.<sup>3–5</sup>

To the correspondents’ specific concerns regarding poor recanalization, the Interventional Management of Stroke (IMS) III study showed a recanalization rate of 78.3% for M2 occlusion, with 72.3% modified TICI 2–3 and approximately 40% modified TICI 2b–3 reperfusion rate. However, in IMS III, revascularization (recanalization and reperfusion) had no interobserver agreement for distinction between modified TICI 2–3 and 2b–3 reperfusion versus outcome and did not correlate to good clinical outcome for M2 occlusion. We encourage the stroke community to settle these discrepancies with the correspondents’ assumptions in future analyses.

More importantly, however, the correspondents disagree with our departure from strict anatomic categorization of the occlusion site in our manuscript. To be sure, we take no issue with Fischer’s and others’ anatomic definitions.<sup>6,7</sup> Nothing could be more direct and succinct than “M1, M2, M3, and M4.” However, the definitions were derived before angiography and intervention were envisioned and were not designed to specifically meet the need to correlate arterial occlusion branching patterns with clinical outcome after intervention by intravenous or intra-arterial drugs or devices. Reference to Goyal’s publication as a resource for the definition of M1–M2 anatomy fails to recognize the prior sharing of a number of emails, images, and documents between us in discussing the M1–M2 issue or his approval as a coauthor of our M2 manuscript after a very long, arduous editing process. Goyal’s anatomic recommendation and our functional modifications constitute 2 different reporting models of varying complexity, purpose, and significance, neither perfect for all circumstances.

None of the correspondents’ references address any perceived anatomic versus physiologic MCA occlusion concerns before 1994. With no applicable treatments to apply, no controversies of parameters within patient study groups would be anticipated. However, between 1994 and 2014, a concern arose regarding the M1 and M2 definition in the Emergency Management of Stroke (EMS) Study<sup>8,9</sup> and its subsequent IMS I,<sup>10</sup> II,<sup>11</sup> and III<sup>2</sup> suc-

sors, culminating in the view that an M1 occlusion would have no M2 segments or distal cortical distribution filling. EMS struggled with the seeming contradiction of terms suggesting that any patent M2 segment, division, branch, artery, or vessel flow should exist with M1 occlusion. M1 occlusion should have 100% of the MCA cortical distribution occluded, save for the classic anterior temporal artery. After all, can, or should, outcome comparisons be made between an M1 occlusion with no distal filling versus an M1 occlusion with distal cortical flow reducing volume at risk, adding collateral circulation, and reducing collateral need from other sources? To compare clinical outcomes, nothing seemed more elemental than defining M1 occlusion as a blockage associated with the absence of arterial filling other than that of a typical anterior temporal artery. Conversely, if 100% of the MCA distribution is not occluded, but rather a branch is patent, coursing into the insular and Sylvian cistern to supply brain beyond, the EMS-IMS functional designation of some form of M2 occlusion becomes operational. The problem of classifying the nature of the M2 occlusion then arises. This conceptual, operational dilemma always lurked in the background of EMS-IMS case evaluation, but returned to the forefront in IMS III, where 83 “M2” occlusions were encountered, with up to 25% exhibiting characteristics easily confused with anatomic M1 occlusion.

Before EMS, no controlled, randomized trial had wrestled with the question of anatomic versus functional occlusion from an endovascular standpoint. PROACT (Prolyse in Acute Cerebral Thromboembolism), conducted concurrently with EMS and reported sequentially from the same podium,<sup>12</sup> did not specifically define M1 and M2 occlusion to address any issue of anatomic concern or to give direction for the future.<sup>13</sup> Having now analyzed the interesting discrepancies subsequently in prospective core-lab analysis of over 100 EMS-IMS M2 occlusions, in addition to many additional trial and nontrial cases, our manuscript hoped to share a succinct method for describing M1, M2, and hybrid cases should such categorization prove of value. With insufficient foresight regarding all the issues that would arise in the final IMS III adjudication, only a post hoc analysis promised to offer clarity regarding our hypotheses and observations.

Even then, to distinguish between M1 and M2 trunk occlusions functionally could have been irrelevant with no significance in doing so, or even erroneous, contributing to another dead wake tailing behind the IMS study. To the contrary, our exploratory analyses suggested that distinctions between distal M1 and M2 trunk occlusion may have relevance, as we very preliminarily reported. A post-post-hoc analysis further exploring unrecognized factors that might contribute to measured numeric differences in the clinical outcome of M1 versus M2 trunk occlusion has been performed. In a presentation at the recent ASNR meeting, we reported a variance in imaging core lab–defined ASPECTS (Alberta Stroke Program Early CT Score) ischemia of the lenticular nucleus (more frequent with M2 trunk occlusion versus distal M1) and insula (less frequent with M2 trunk occlusion versus distal M1). Recognizing that our original post hoc analysis identified at least 30%–40% of M2 trunk occlusions had occluded lateral lenticulostriate arteries arising from them, an associated deep ischemic effect is understandable. In addition, less frequent insular infarction with M2 trunk occlusion further supports our

hypothesis that better collateral flow may indeed be afforded by patent posterior temporal or holotemporal branches. However, these 2 observations would create direct but opposite effects on good clinical outcome, perhaps neutralizing one another in the mRS outcome metric. We would welcome review by the investigators of the smaller recent studies detailed in the letter's table to support or summarily refute our observations.

Finally, the correspondents themselves also appear to find the historical anatomic classification insufficient, suggesting their own new subgroup classification. Their classification addresses issues not directly specific to our manuscript, apart from our simple, general schematic reproduced with their letter. We will not comment on their individual details and depictions. The lack of core lab data and numbers of the varieties of occlusions envisioned provides little perspective on the impact their categorization would provide. However, that "a distal M1 occlusion with a large anterior temporal artery supplying the entire temporal lobe" should not be contracted to "M2 trunk occlusion" seems uneconomical in effort, inflexible in practice, less predictive in comparison of outcomes, and generally less precise in understanding. To use "M1-like" or "M2-like" evades the precision or exactness of what something is in favor of what it seems to be.

Workers interested in greater understanding of less obvious patient-related factors contributing to the clinical outcome after stroke intervention should be open to modifications not envisioned by or on the viewing screens of our predecessors. Perhaps we should ask ourselves, given the advances in the treatment of cerebrovascular disease, where our anatomist ancestors would stand on the issue of splitting or clarifying their anatomic construct. Would they be as flexible as our new clot-removal devices and recognize that new observations on anatomy versus outcome might have sufficient relevance to recommend modifying their construct, or would they be rigid and inflexible, holding to the dictates of their time-honored effort? As a world-renowned empirical observer, radiologist Dr. Benjamin Felson used to summarize, when confronted with controversy and/or disagreement, "My mind's made up. Don't confuse me with the facts."

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