Response by Bivard et al to Letter Regarding Article, “Impact of Computed Tomography Perfusion Imaging on the Response to Tenecteplase in Ischemic Stroke: Analysis of 2 Randomized Controlled Trials”

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We thank Roozenbeek and colleagues for their interest in our recent work.[1] The clinical significance of the ischemic penumbra in patients treated with intravenous thrombolysis is well established.[2] The term mismatch has become colloquially used to describe the situation where the relative volume of a patient’s infarct core is less than the total perfusion lesion, thus representing the penumbra. Target mismatch is simply a way of defining a group of patients with a relatively large penumbra that is salvageable from infarction with effective reperfusion. In patients without such a target mismatch, there is limited brain tissue to salvage, and this translates clinically into less benefit from reperfusion.[3] Therefore, we believe that clear biological plausibility exists for treating patients with target mismatch, and we explored this hypothesis in our analysis. We agree that secondary analyses of pooled data must be regarded with caution and that 1 appropriate statistical approach is to seek evidence of a perfusion profile-treatment group interaction. In this exploratory secondary analysis, one would not expect to find robust evidence of such an interaction. This outcome could only be derived from an appropriately designed clinical trial of sufficient sample size, which is not currently available from either the intravenous or endovascular trials. We believe, however, that the findings of our pooled analysis support the possibility that improved reperfusion seen with tenecteplase translated into better clinical outcomes in patients with more tissue to salvage (ie, target mismatch patients). Our findings offer support to the possibility that tenecteplase might have advantages over existing thrombolytic therapy with alteplase and yield some preliminary estimates of treatment effect sizes in patients selected by target mismatch profile compared with unselected cases or those without target mismatch, which is of benefit in the design of future clinical trials. We certainly agree that our analysis was underpowered to detect a weaker treatment effect.

Finally, we must thank Roozenbeek and colleagues for their mention of the need for phase III trials.[1] Debates will always take place about trial design in stroke and whether to include all patients (lumping) or select those most likely to benefit from the intervention (splitting).[4] For the selection of patients for thrombectomy, for example, the lumping approach taken in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) may lead to futile treatment with health economic impacts that even the wealthiest economies could not absorb. The splitting approach to patient selection used in EXTEND IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial) or SWIFT-PRIME (Solitaire With the Intention For

Thrombectomy as PRIMary Endovascular Treatment) may be a more cost-effective approach.[5] Time will tell. Because we are all for freedom of choice, our teams based in Australia and Scotland are currently undertaking the TASTE trial (Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation) and the ATTEST 2 trial (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis 2), respectively. TASTE uses target mismatch selection criteria, whereas ATTEST 2 has broader inclusion criteria. Both will examine the question of whether intravenous tenecteplase leads to superior outcomes compared with intravenous alteplase in acute ischemic stroke. We would like to extend a warm invitation to our colleagues to participate in either (or both) trials.

References

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