

## COMMENTARY

# Should the extent of infarction modify the decision to use bridging thrombolytic prior to endovascular thrombectomy?

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Email: [bruce.campbell@mh.org.au](mailto:bruce.campbell@mh.org.au)**Keywords:** computed tomography angiography, endovascular treatment, ischaemic stroke, thrombolysis

Six randomized trials have examined the benefit and risk of bridging thrombolytic administration versus direct endovascular thrombectomy (EVT) in patients who can immediately access EVT [1–6]. Two trials performed in China met their prespecified non-inferiority criteria [1,2] but others reported functional outcome trends in favour of bridging thrombolytic [3–5] and overall there was a relatively small magnitude increase in symptomatic intracerebral haemorrhage. Asian patients in the Randomized Controlled Trial of Direct Endovascular Clot Retrieval versus Standard Bridging Thrombolysis with Endovascular Clot Retrieval within 4.5 h of Stroke Onset (DIRECT SAFE) trial appeared to have significant benefit of bridging thrombolytic [5].

Given these mixed results, some experts have suggested that an individualized, precision medicine approach to the use of intravenous thrombolytic is required when thrombectomy is immediately available. Ultimately, the planned individual patient data meta-analysis of all six trials will provide the most useful insights on this matter. It is currently unknown whether a sub-population of patients who benefit from direct thrombectomy can be identified and, importantly, whether these patients can be treated using a direct approach without creating a deleterious delay in intravenous thrombolytic for the majority of patients. An additional consideration is whether improved thrombolytics, for example tenecteplase, which appeared to be not just non-inferior but superior to alteplase prior to endovascular thrombectomy [7], alter the risk–benefit seen in these alteplase-based trials.

In this issue, Jia et al. report a sub-analysis of the Direct Intraarterial Thrombectomy to Revascularize Acute Ischemic Stroke

Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals (DIRECT-MT) trial [8]. The authors examine whether the extent of ischaemic injury on the pre-treatment computed tomography (CT) brain (assessed using the Alberta Stroke Program Early CT Score, ASPECTS) modified the effect of the direct versus bridging treatment strategy. Patients with extensive non-contrast CT changes are one of the commonly proposed subgroups who may benefit from direct thrombectomy and can readily be identified without delaying standard thrombolytic decision-making, unlike other candidate selection characteristics, for example the requirement for stent implantation. The hypothesis is that patients with more extensive ischaemic injury will have greater risk of haemorrhagic transformation when thrombolytic is administered and therefore have improved outcomes with direct EVT.

DIRECT-MT, performed at 41 centres in China, was the largest of the six trials and enrolled 656 patients. Overall, the common odds ratio (OR) for ordinal analysis of the modified Rankin scale (mRS) was 1.07 (95% confidence interval [CI] 0.81–1.40), the lower 95% CI >0.80 meeting the prespecified non-inferiority margin for direct thrombectomy. Functional independence (mRS 0–2) occurred in 36.4% of direct and 36.8% of bridging patients (adjusted OR 0.97, 95% CI 0.68–1.37). In the present sub-analysis, 56/649 (9%) patients had ASPECTS 0–4. Although, as the authors indicate, ASPECTS has limited correlation with infarct volume, on average these patients have larger infarcts than the ASPECTS 6–10 group. There was no statistically significant interaction of ASPECTS with direct treatment strategy, although that analysis may be underpowered. However, the absolute proportion of patients achieving mRS 0–2 in the ASPECTS

See paper by Z. Y. Jia et al. on page 1643.

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0–4 group was 3/25 (12%) in the direct group and 5/31 (16%) with bridging thrombolytic (OR 0.76, 95% CI 0.15–3.88) so there was no suggestion of worse outcomes due to thrombolytic, noting the wide confidence intervals. Interestingly, symptomatic intracerebral haemorrhage was not more frequent in the low ASPECTS group overall (2/56, 3.6%) versus higher ASPECTS (32/593, 5.4%), and there was no difference in symptomatic intracerebral haemorrhage between bridging and direct treatment strategies in the ASPECTS 0–4 subgroup (1/25 direct vs. 1/31 bridging).

Other direct thrombectomy trials have reported subgroup effect by ASPECTS category: the Direct Endovascular Thrombectomy vs. Combined Intravenous Thrombolytic and Endovascular Thrombectomy for Patients with Acute Large Vessel Occlusion in the Anterior Circulation (DEVT) [2] and Direct Mechanical Thrombectomy in Acute Large Vessel Occlusion Stroke (SKIP) [6] trials dichotomized ASPECTS <8 versus 8–10 and found no treatment effect heterogeneity, but also no hint of detriment of thrombolytic in patients with lower ASPECTS based on point estimates, acknowledging that patients with ASPECTS 0–4 were not included in SKIP and the proportion in DEVT was not reported.

In conclusion, current data have not supported the hypothesis that patients with extensive ischaemic changes benefit from omitting thrombolytic prior to thrombectomy, emphasizing the importance of verifying attractive hypotheses with data. Individual patient data meta-analysis to obtain the most accurate interpretation of all the available data is particularly critical for this important clinical question. Pending those results, clinicians can take some comfort from this study that continuing to administer thrombolytic prior to thrombectomy does not appear to harm patients with extensive ischaemic injury.

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#### CONFLICT OF INTEREST

None.

#### AUTHOR CONTRIBUTION

Bruce C. V. Campbell: Conceptualization (lead); formal analysis (lead); writing—original draft (lead).

#### DATA AVAILABILITY STATEMENT

No original data are presented in this article.

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