Thrombectomy for Stroke at 6-16hrs with Selection by Perfusion Imaging

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At the time of this trial, prior studies had supported the efficacy of endovascular thrombectomy (EVT) for the treatment of large vessel occlusions, if performed within 6hrs of stroke symptom onset (i.e., MR CLEAN). Further, the recently-published DAWN trial had also shown the benefit of extended-window EVT (i.e., 24hrs of a LKN), if patients were selected based on the presence of a significant clinical deficit out of proportion to the size of the core infarct seen on imaging. Finally, other trials had highlighted the efficacy of CT or MR perfusion imaging for the purpose of identifying the core infarct separate from the ischemic penumbra, suggesting the utility of this technique for identifying patients with salvageable tissue (via EVT), even if presenting long after symptom onset. As such, the goal of DEFUSE 3 was to assess the efficacy of EVT when performed within 6-16hrs following symptom onset, and when selecting patients based on the presence of salvageable brain tissue identified via CT or MR perfusion imaging.

Experimental design and statistics: This study was a randomized, open-label trial with blinded outcome assessments, conducted across 38 centers in the US. Patients were eligible for enrollment if they were able to undergo EVT within 6-16hrs after stroke symptom onset, and if CTA/MRA imaging identified an occlusion of the cervical or intracranial ICA or the proximal MCA[1]. In addition, perfusion imaging inclusion criteria (via RAPID software, **Fig 1**) included 1) a core infarct volume <70mL, 2) a mismatch ratio (ischemic: infarcted tissue) $\geq$1.8[2], and 3) a penumbra of $\geq$15mL. Patients who met eligibility criteria were randomized 1:1 to receive either EVT with standard medical therapy vs. standard medical therapy alone. EVT was performed with any FDA-approved device, groin puncture had to occur within 90min after imaging, IV tPA was allowed prior to EVT, but intra-arterial tPA was not allowed[3]. Clinical assessments were performed at baseline, 24hrs post randomization, at discharge, at 30d (blinded), and at 90d (blinded). The primary efficacy outcome was the mRS score at 90d, and the secondary efficacy outcome was functional independence (mRS of 0-2) at 90d. Primary safety outcomes included death at 90d and symptomatic ICH (sICH) at 36hrs. Several imaging outcomes were also assessed. Statistically, the primary outcome was assessed via the use of ordinal regression.

Results: The planned enrollment for this trial included 476 patients. However, as this trial co-occurred with the DAWN trial, itself showing clinical benefit of EVT at 6-24hrs, early interim analyses were performed and enrollment was terminated early due to high efficacy. With this, a total of 182 patients underwent randomization here, with n = 92 to EVT and n = 90 to medical therapy. Baseline characteristics between the 2 groups were similar (**Table 1**), including a median time to qualifying imaging of ~10hrs. In terms of the primary outcome, EVT was associated with a more favorable distribution of disability scores on the mRS (OR 2.77, $p< 0.001$), with 45% of patients in this group achieving functional independence at 90d (mRS 0-2), vs only 17% in the medical therapy group (risk ratio of 2.67, $p< 0.001$; **Fig 2, Table 2**). Further, mortality at 90d was 14% in the EVT group but 25% in the medical therapy group ($p = 0.05$), and rates of sICH did not differ (7% in EVT, 4% in medical therapy; $p = 0.75$)[4]. EVT yielded a TICI score of 0 in 11%, 2a in 13%, 2b in 57%, and 3 in 19% of patients[5]. Other

[1] Other major inclusion criteria included age 18-90, NIHSS $\geq$6, mRS < 2; see supplementary appendix

[2] Size of penumbra estimated based on amount of tissue with a Tmax of >6sec

[3] For those with ICA stenosis or occlusion, angioplasty or stenting was permitted

[4] EVT-related complications occurred in only 2 patients within this group

[5] TICI 0 = no perfusion beyond occlusion, 2a = filling in <2/3 of vascular territory , 2b = complete filling but slower than normal, 3 = complete reperfusion

imaging outcomes are shown in Table 2, and subgroup analyses (limited based on small N's) are shown in **Fig 3**, with no clear heterogeneity of the treatment effect based on subgroup.

Conclusions: DEFUSE 3 effectively showed that EVT, if performed within 6-16hrs of symptom onset and in patients with salvageable brain tissue identified via perfusion imaging, resulted in significantly better functional outcomes at 90d as compared to standard medical therapy. Despite numerically higher rates of sICH with EVT, mortality rates were still lower with EVT. Notably, previous EVT trials had suggested a limited benefit of EVT if instituted >7-8hrs after symptom onset, though DEFUSE 3 differed from these trials in their use of perfusion imaging to identify patients with salvageable brain tissue that could benefit from reperfusion. Moreover, even despite underpowered subgroup analyses here, these analyses still suggested that the efficacy of EVT was similar in patients treated >12hrs after symptom onset. Finally, it is worth noting that the treatment effect of EVT here was better than that in prior trials treating patients within 6hrs of symptom onset, though much of this could have been related to the lower rates of favorable outcomes in the medical therapy group here, leading to a larger treatment effect. This could have been at least partially related to the lower rates of tPA use in the medical therapy group in DEFUSE 3, given enrollment eligibility of 6-16hrs after symptom onset. Regardless, DEFUSE 3 provided promising data, and served as a landmark study both in practice and to guide other similar trials since.