DEFUSE 3: Second Trial Supports Late Thrombectomy in Stroke

Sue Hughes

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LOS ANGELES — A second randomized trial has shown impressive clinical benefit of thrombectomy in patients with a large-vessel occlusion ischemic stroke presenting late, after the traditional 6 hours from stroke onset that this technology is currently used.

The National Institutes of Health–funded DEFUSE 3 trial was presented here at the International Stroke Conference (ISC) 2018 and simultaneously published online in the *New England Journal of Medicine*.

Results showed that in patients presenting 6 to 16 hours after stroke onset (or last seen well) who fulfilled the imaging criteria for the trial, removing the clot with an endovascular thrombectomy procedure was associated with significantly better 90-day functional outcomes than control patients.

"Our results show that nearly half of the patients who had the thrombectomy procedure were saved from the devastation and disability of the stroke," lead investigator of DEFUSE 3, Gregory Albers, MD, Stanford University Medical Center, California, said.

"People were assuming that we would have much more modest benefits because we were treating patients so much later," he added. "But our results actually show that the treatment benefit is even more significant and clinically important than in trials of earlier intervention."

"We now know that every stroke evolves in a unique manner and this is not just to do with time," Dr Albers said. "The old mantra that 'time is brain' and nothing can be done if patients present after 6 hours is no longer valid. By analyzing imaging profiles, we can identify patients with salvageable brain tissue who can still benefit to a dramatic degree much later."

The primary outcome of the DEFUSE 3 trial was the difference in the ordinal score on the modified Rankin scale (mRS) at 90 days, an overall assessment of disability. The odds ratio for a more favorable mRS score in the thrombectomy group was 2.77.

"This is the largest odds ratio ever reported for a thrombectomy study, so it indicates a major benefit," Dr Albers stated. "When we control for minor imbalances between the groups, the odds ratio increases even more to a really staggering 3.36."

The DEFUSE 3 results complement those of the DAWN trial reported last year, in which similar benefits were seen in patients presenting 6 to 24 hours after stroke onset. DAWN investigator Jeff Saver, MD, University of California, Los Angeles, commented on the new findings for *Medscape Medical News*.

"The DEFUSE results are very similar to the DAWN findings," Dr Saver said. "DAWN showed a shocking degree of benefit. But it was just one trial — the world was waiting to see if this was a chance finding or was real. DEFUSE 3 found the same shocking degree of benefit. This shows the DAWN result was real — using biology works to identify patients who benefit from thrombectomy long after the traditional time cutoffs. That is great news."

The trials differed in some small ways in terms of inclusion criteria, he noted, "but these are very fine points. The two trials are actually strikingly similar in terms of what they were trying to achieve and what they showed."

From Presentation to Guidelines in Just 2 Hours

The new studies also featured extensively in the new treatment guidelines for acute ischemic stroke issued at the ISC meeting on the same day as the DEFUSE 3 results were announced.

"We anticipate that the DEFUSE 3 results will have an immediate impact on clinical practice," Dr Albers said. "We were able to provide an embargoed copy of our study to the guidelines group, so we have a potentially 'once in a lifetime situation' where a study gets presented for the first time and within 2 hours is included into new clinical guidelines."

The DEFUSE 3 trial included 182 patients with a large-vessel occlusion ischemic stroke presenting 6 to 16 hours after stroke onset or last known well who underwent imaging with computed tomography perfusion or magnetic resonance diffusion/perfusion.

The trial used an automated software program (RAPID) to determine whether patients fulfilled the requirements for target mismatch — when there is a relatively small area of brain tissue that has already died (core, in this case less than 70 mL) but a large area of tissue that is threatened but potentially salvageable. The trial required a mismatch ratio (the ratio of the volume of ischemic tissue on perfusion imaging to infarct volume) of 1.8.

Patients who met both clinical and imaging selection criteria were randomly assigned 1:1 to endovascular therapy plus medical management or medical management alone. The individual endovascular therapist chose the specific thrombectomy device.

The trial was stopped early by the data safety monitoring board because of a high likelihood of benefit in the endovascular group, after the DAWN results were reported.

The primary endpoint was the distribution of scores on the modified Rankin Scale (mRS) at day 90. The unadjusted odds ratio for a more favorable score in the thrombectomy group was 2.77 (95% confidence interval [CI], 1.63 - 4.70; *P* < .001). After adjustment, this became 3.36 (95% CI, 1.96 - 5.77; *P* < .001).

The secondary endpoint was the proportion of patients with mRS scores of 0 to 2 at day 90, which was achieved by 45% of in the endovascular group vs 17% in the control group (*P* < .0001).

Dr Albers said, "These patients may have a mild deficit but essentially they live a normal life — this is an excellent outcome."

At the other end of the spectrum, mRS scores of 5 or 6 occurred in 22% of the thrombectomy group vs 42% of the control group (*P* = .0048). Dr Albers said, "Scores of 5 or 6 in the mRS scale are the most feared outcome of stroke — death or being completely dependent on others in a nursing home. Patients treated with thrombectomy in DEFUSE 3 show an unprecedented improvement in these worst possible outcomes."

The full mRS results show that the benefits of thrombectomy are evident across all stroke severities.

Dr Albers said the "spectacular" results in the treated patients reflected the devastating effects of a major stroke in the control group. "The control arm had very poor outcomes. Only one in every six patients (16%) had a good outcome (mRS 0 to 2), so five out of every six patients had bad outcomes with 26% dead, and 16% were completely disabled, needing nursing home care."

Table. DEFUSE 3 Results by Individual mRS Scores

mRS at 90 d	Control Group (%)	Endovascular Therapy Group (%)
0	8	10
1	4	16
2	4	18
3	16	15
4	27	18
5	16	8
6	26	14

Dr Albers noted that about half the patients in DEFUSE 3 had a "wake up" stroke, that is, they were discovered to have had a stroke on waking up, so the exact time of symptom onset is not known.

"It is therefore important to look closely at the witnessed stroke patients. The median time to randomization in witnessed stroke patients was 10 hours. The benefit of thrombectomy in this group was essentially identical to those who woke up with a stroke. The odds ratio for a positive effect on the ordinal mRS is 3.4 in both. So this shows that the benefit was seen not because we are treating patients in a shorter time from what we had anticipated."

Dr Albers elaborated that the impressive clinical benefits reflected greater rates of the reperfusion in the endovascular group: 79% vs 18% in the control group.

The main side effect of concern, hemorrhagic stroke, occurred in 6.5% of the thrombectomy group vs 4.4% of the control group (*P* = .75).

"There is concern about causing bleeds as a result of pulling these clots out — and there was a tiny trend, but this was not significant," Dr Albers commented.

More details on differences between the DEFUSE 3 trial and the DAWN trial and how both trials can be interpreted together and applied to clinical practice will be discussed in a separate *Medscape Medical News* article.

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