



A new DAWN for extended window thrombectomy in ischemic stroke: an editorial on the DAWN trial

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Stroke is one of the leading causes of long-term disability in the United States and around the world (1). Most of all strokes are ischemic, in which the brain's blood supply is obstructed. In the majority of stroke survivors greater than 65 years old, this can significantly impact their independence and mobility (1). Clinical trials in stroke have been designed to reduce mortality and morbidity in populations at high risk. Patients arriving at a hospital within 3–4.5 h of their symptom onset can qualify for acute thrombolysis which leads to improved function after a stroke (2). Considered the gold standard in acute stroke therapy, IV-alteplase is the only FDA-approved treatment for ischemic strokes, but needs to be used within a limited therapeutic time window.

This limited treatment window has led to interest in endovascular therapy to extend the treatment window for acute ischemic stroke. In 2015, five randomized clinical trials searched for efficacy of mechanical thrombectomy in patients with acute stroke caused large vessel occlusion in the anterior circulation (3). Their findings demonstrated that critical imaging analysis, workflow modification, and newer generation thrombectomy devices were beneficial in treatment of ischemic stroke using endovascular treatment over standard medical care. These trials changed guidelines that endovascular treatment is a highly effective therapy across all subgroups if performed within 6 hours of stroke presentation. Of the 5 trials, only 2 had therapy windows beyond 6 h. The REVASCAT trial recruited eligible patients within 8 h after the onset of symptoms (4). Results showed thrombectomy within 8 h of onset, reduced the severity of disability and higher rates of functional

independence. However, over 87.4% of their treatment groups were performed within 6 h. The ESCAPE trial enrolled up to 12 h after symptom onset with a small infarct core. Their median time from stroke onset to treatment reperfusion was about 4 h (5). Despite these two trials, there was insufficient evidence that endovascular therapy window beyond 6 h had significant treatment effect to limit disability.

The DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial was designed to answer two lingering questions: (I) the unclear benefit of endovascular treatment beyond 6 h and (II) how to carefully select for patients based on a clinical-radiologic mismatch to salvage with reperfusion therapy (6). The DAWN clinical trial is an international, randomized controlled research study investigating the benefits of thrombectomy 6–24 h after stroke onset. Instead of looking at penumbral volume or only stroke lesion burden, DAWN investigators selected patients based on a clinical-radiologic mismatch. Patients were selected based on three groups. The first was ≥ 80 years old, National Institutes of Health Stroke Scale (NIHSS) ≥ 10 , and core volume infarct < 21 cc. The second group was < 80 years old, NIHSS ≥ 10 , and core infarct volume < 31 cc. Finally, the last group was < 80 years old, NIHSS > 20 , and core infarct volume of 31–51 cc. Patients meeting these criteria could then be randomized 1:1 to either thrombectomy or medical control therapy. DAWN was conducted across 26 centers in Europe, Australia, the US, and Canada. The study enrolled a total of 206 patients from September 2014

through February 2017. To qualify as a participating center, ≥ 40 mechanical thrombectomy procedures had to be performed annually at the centers. Dedicated stroke or neurointensive care units would also be required to admit enrolled patients. Local institute guidelines directed medical care if patients did not qualify for thrombectomy. Patients were followed for 90 days and the primary efficacy endpoint was assessed via utility-weighted modified Rankin Scale (mRS) and dichotomized mRS. The dichotomized mRS was originally a secondary outcome, but the investigators were asked by the FDA to change to a primary outcome. Choosing utility-weighted mRS for disability after stroke over traditional mRS was meant to address some concerns over limitations of power with the traditional mRS. Utility-weighted mRS is theoretically thought to capture better treatment effects and maintain statistical power while improving scale interpretability then when analyzed ordinally (7). The median baseline NIHSS score in their cohort was 17 for both groups. The first primary endpoint for the utility-weighted mRS at 90 days for the thrombectomy group was 5.5 versus 3.4 in the control group, with higher numbers representing better outcomes. In the second primary endpoint, 48.6% of thrombectomy patients were independent at 3 months compared to 13.1% in the medical arm. The rate of symptomatic intracranial hemorrhage nor 90-day mortality did not differ significantly between the study groups.

While the results are extremely favorable for treating ischemic stroke up to 24 h in a carefully selected group of patients, there are still concerns. A major question of the study is that investigators did not report screening numbers in how many patients would truly present with the trial's selection criteria. If new thrombectomy centers are to be created based on DAWN results, there remain several questions as to if creating a better system of care would be more beneficial. Establishing new centers performing thrombectomy procedures require a lot of resources including: a specific perfusion software used in this study (RAPID) that can be cost-prohibitive; dedicated stroke units and neurointensive units are also critical in improved outcomes. The centers in this study also required a certain amount of expertise to obtain these improved outcomes. Mechanical thrombectomy is associated with intra-procedural or post-operative complications, which need to be minimized and effectively managed to maximize the benefits of thrombectomy. Procedural complications include: access-site problems (vessel/nerve injury, access-site hematoma, and groin infection); device-related

complications; symptomatic intracerebral hemorrhage; subarachnoid hemorrhage; embolization to new or target vessel territory. Some complications are life-threatening, and many lead to increased length of stay in intensive care and stroke units. Complications increase costs and delay the commencement of rehabilitation. Fortunately, in the results, it seems that complication rates are similar between the two treatment complications. However, these issues point to the importance in determining whether creating new systems of care and centers based on current DAWN data is a practical use of resources to better select for patients within the extended treatment period. More information is needed in how often patients meet DAWN inclusion criteria before generalizing results and forming new guidelines for treatment.

The results from DAWN are truly positive and potentially game-changing and safe for treatment of select ischemic stroke patients presenting up to 24 h. With future extended-window interventional trials on the horizon, including DEFUSE-3, changes in stroke treatment guidelines will likely be forthcoming again. If we can determine how many stroke patients can benefit from these results, we can start developing better care that includes improved access to imaging (CT head, CT angiogram, and CT perfusion imaging) and selecting patients appropriate for endovascular treatment. CT angiography is not routinely available in all hospitals. Perfusion imaging for acute stroke is also not routinely done, even in stroke centers, and typically requires selection for high-risk large vessel occlusion patients. Further studies need to be done on how many centers offer 24 h endovascular clot retrieval and its geographic distribution. The prospect of receiving mechanical thrombectomy for acute stroke is associated with geographic proximity and how close people are to hospitals offering this treatment. Changing treatment window time will allow patients who were excluded for unknown reason or late arriving for medical care to still benefit from thrombectomy. Faster time to treatment remain critical for the achievement of the best possible outcomes. Thrombectomy is safe with careful selection of patients and in experienced operators with a dedicated interventional team. Therefore, thrombectomy delivery will need to continue to improve in both specific centers and their systems of care with teams.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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