Late Window Paradox

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The mantra of acute stroke therapy, time is brain is a call to arms that motivates both the public and medical practitioners to treat stroke as a time-critical emergency. Countless articles have documented inexorable declines in favorable clinical outcomes associated with delayed administration of thrombolytic or endovascular therapies. Therefore, one would naturally anticipate that the benefits of endovascular therapy would be markedly more modest if treatment is delayed many hours beyond the guideline-recommended 6-hour therapeutic window. How then do we explain the remarkably robust results of DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) and DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo), 2 recently published trials of endovascular therapy initiated up to 16 to 24 hours after patients were last known well?

Larger Benefits With Later Treatment

DAWN randomized patients at a median of 12.5 hours from onset and documented the largest absolute increase in functional independence ever reported in any acute stroke treatment trial, 35.5%.[1] DEFUSE 3 randomized patients at a median of 11 hours after onset and documented a 28% increase in functional independence and an additional 20% absolute reduction in death or severe disability, which represents the largest reduction in mortality/severe disability ever achieved.[2] By comparison, the pooled analysis of 5 modern early window thrombectomy trials (HERMES [Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials]) revealed an absolute increase in functional independence of 19.5% and a reduction in mortality/severe disability of 11%[3] (Figure 1). Both early and late window studies included patients of similar ages, baseline National Institutes of Health Stroke Scale scores, and vessel occlusion sites. Patients were treated with the same modern thrombectomy devices and reperfusion was achieved in similar proportions of patients in the endovascular arms of the early and late window studies. So why was the treatment effect larger in the late window trials?

Explaining the Paradox by Understanding Stroke Evolution

An understanding of the evolution of ischemic core lesions and the imaging-based selection criteria used in these studies offers an explanation for the apparent paradox. Several studies have performed magnetic resonance imaging scans on stroke patients with large artery occlusions at various time points after symptom onset. These studies have consistently documented that the growth of early diffusion-weighted imaging (DWI) lesions (which provides a reliable estimate of the ischemic core) varies substantially between patients.[4] Some patients, typically individuals with very poor collaterals, develop very large DWI lesions within 2 to 3 hours, whereas other patients have little or no DWI lesion growth for 12 hours or longer. Although some fortunate patients never develop a large infarct despite a persistent large artery occlusion, the vast majority of the slow growers with large vessel occlusions will eventually develop an extensive infarction. However, it typically takes 3 days for the maximum DWI volume to be achieved in nonreperfused patients.[4,5]

The DEFUSE 2 study (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2) assessed DWI growth rates in patients with middle cerebral artery or internal carotid artery occlusion.[4] Remarkably, ≈50% of these patients had very slow early growth rates, with DWI volumes <10 to 15 mL, even when first imaged ≥10 hours from symptom onset (shown in green in Figure 2). Other studies have also documented a very high rate of stable DWI volumes during the early hours after stroke. For example, Gonzalez et al[6] demonstrated that the majority of nonreperfused patients with acute stroke have no increase in the size of the DWI lesion volume when a second DWI scan is performed 4 hours after the baseline scan.

About 30% of DEFUSE 2 patients fell into the medium growth range (yellow overlay) with growth rates of ≈3 to 10 mL/h and only ≈20% fell into the malignant rapidly growing red category, with growth rates ranging from about 15 mL/h to as high as 100 mL/h[4] (Figure 2).

Early Window Trials With No Restrictions on Infarct Core Size

Consider the recent early window thrombectomy trials, that treated patients within 5 hours THRACE (Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke)[7] or 6 hours MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)[8] of stroke onset, and

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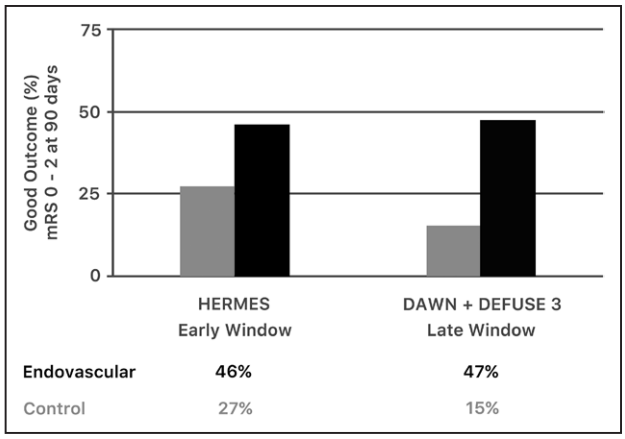

Figure 1. Favorable outcome rates in early vs late window thrombectomy trials. Note that good outcome rates in the late window vs early window trials are similar in the endovascular groups, but the outcomes are less favorable in the control groups of the late window trials. Therefore, the treatment effect is larger in the late window studies (absolute increase in modified Rankin Scale score of 0–2, 19% early window vs 32% late window, P=0.006, Breslow–Day test). The HERMES study[3] pooled the results of 5 early window endovascular trials. DAWN indicates DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; and HERMES, Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials.

did not assess the size of the baseline ischemic core. These trials likely enrolled a substantial number of patients in all 3 core growth categories (Figure 2). In these modern early window thrombectomy trials, the time between baseline imaging and when reperfusion was achieved was typically ≈2 hours.[9] For patients in the red category especially those with infarct growth rates >50 mL/h, substantial infarct growth would be expected over that 2-hour period between imaging and reperfusion. Some of these patients likely had already achieved their final infarct volume by the time they were randomized. Others likely completed their infarct between the time of initial imaging and when reperfusion was achieved. In either case, no treatment benefit would be anticipated for these patients with completed infarcts, even if they are successfully reperfused. For patients in the medium growth category, infarct growth between baseline imaging and reperfusion would be anticipated to be modest which likely would lead to a favorable response to reperfusion. For patients in the favorable green category, expected growth between imaging and reperfusion would be minimal and very favorable outcomes anticipated after reperfusion, even if the procedure is challenging and reperfusion is significantly delayed. In the medical therapy arm, patients with large intracranial occlusions who do not reperfuse generally do poorly, especially the red patients with poor collaterals who rapidly develop very large infarctions. Among patients in the medical therapy arms who achieve early reperfusion after tPA (tissue-type plasminogen activator) therapy, outcomes comparable to the thrombectomy group would be expected. The considerations summarized above likely explain the relatively modest absolute benefits documented in THRACE (absolute increase in the rate of achieving an modified Rankin Scale score of 0–2 of 11%) and MR CLEAN (14%).

Early Window Trials With Small Infarct Cores and Salvageable Tissue

Now let us consider the early window trials that restricted enrollment to patients with smaller ischemic core lesions (<50 mL in SWIFT PRIME [Solitaire™ With the Intention for Thrombectomy as Primary Endovascular Treatment Trial] and <70 mL in EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial]).[10,11] Because initial imaging was typically performed at least 2 hours after symptom onset, these trials excluded the

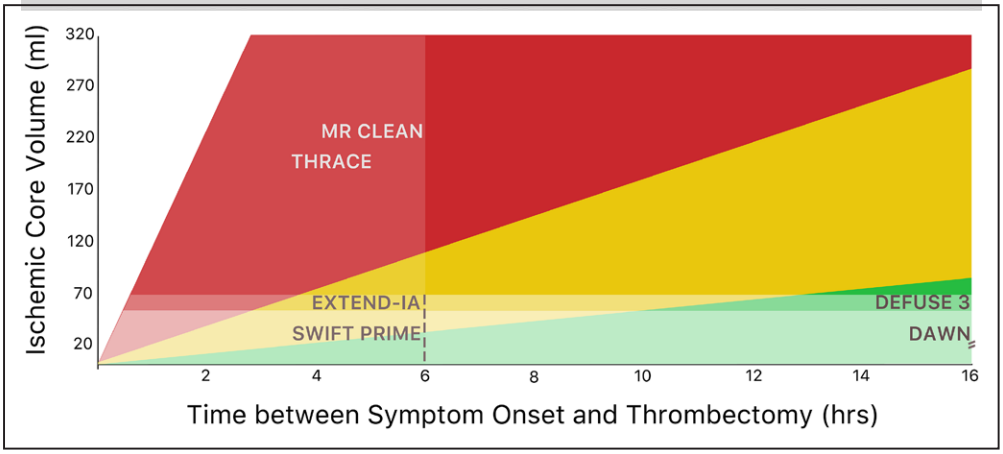

Figure 2. Estimated infarct growth rates in patients with internal carotid artery or middle cerebral artery occlusions. Data regarding ischemic core growth rates over time from DEFUSE 2.[4] As discussed in the text, only ≈20% of patients had rapid early growth rates (red zone), ≈30% intermediate growth (yellow), and ≈50% had slow growth (green zone). Note that the selection criteria for THRACE required thrombectomy be initiated within 5 hours, MR CLEAN within 6 hours. For SWIFT PRIME, the maximum core volume was 50 mL; 70 mL for EXTEND-IA. For DAWN, the maximum core volume was 20 mL, 30 mL, or 50 mL (based on age and National Institutes of Health Stroke Scale score); 70 mL for DEFUSE 3. DAWN treated eligible patients up to 24 hours. DAWN indicates DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; and SWIFT PRIME, Solitaire™ With the Intention for Thrombectomy as Primary Endovascular Treatment Trial.

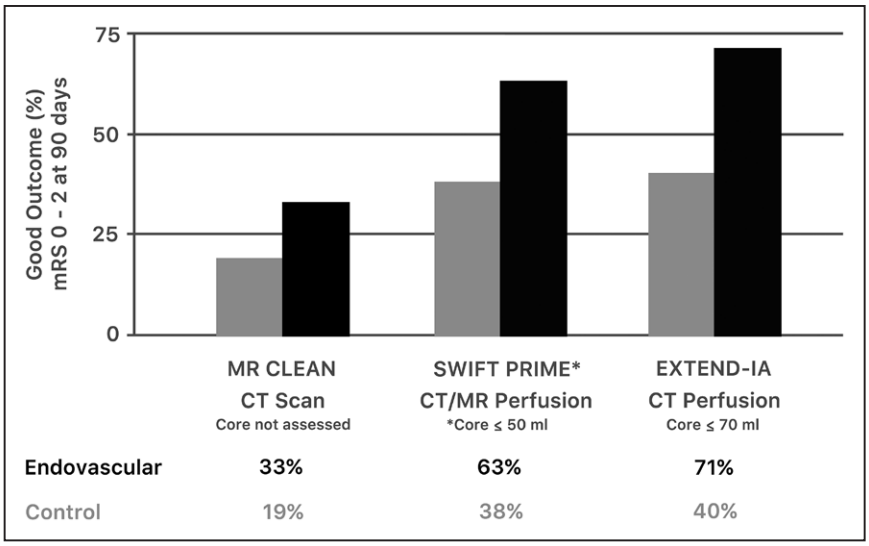

Figure 3. Favorable outcome rates in MR CLEAN vs SWIFT PRIME and EXTEND-IA. Note that favorable outcome rates in both the endovascular and control groups are about twice as large in the 2 trials that excluded patients with larger ischemic core volumes (volumes >50 mL were excluded in SWIFT PRIME and >70 mL excluded in EXTEND-IA). *Data for SWIFT PRIME[12] includes only patients with the target mismatch profile. EXTEND-IA indicates Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; and SWIFT PRIME, Solitaire™ With the Intention for Thrombectomy as Primary Endovascular Treatment Trial.

majority of patients in the red zone and enrolled primarily slow and some medium growth rate patients. Therefore, substantially less growth would be expected during the interval between imaging and reperfusion and overall outcomes would be anticipated to be substantially better. One would also expect the intravenous tPA-only medical arms of the trials to have significantly more favorable outcomes than the MR CLEAN control group because patients with better collaterals are more likely to achieve reperfusion with tPA and the vast majority of the rapid growth patients, who typically have large infarct volumes after intravenous thrombolysis, were excluded. All of the patients in EXTEND-IA, and 80% in SWIFT PRIME, were enrolled based on the target mismatch profile using RAPID software (which requires evidence of salvageable tissue based on a formula that incorporates core infarct size and the volume of hypoperfused tissue on perfusion imaging), and the overall rate of functional outcome in both the thrombectomy and the intravenous tPA groups were about twice as large as in MR CLEAN (Figure 3). The treatment effect of thrombectomy versus intravenous tPA for achieving functional independence (modified Rankin Scale score of 0–2) was also about twice as large. These findings support the role of advanced imaging in early time windows.

Late Window Trials

Finally, let us look at the late window trials, DAWN and DEFUSE 3. DAWN enrolled patients based on a clinical-core mismatch with maximum infarct core volumes of 20, 30, or 50 mL, depending on patients' age and National Institutes of Health Stroke Scale score.[1] DEFUSE 3 used a hypoperfusion-core mismatch and allowed core volumes up to 70 mL as long as there was a substantial volume of salvageable tissue evident on perfusion imaging.[2] Similar to EXTEND-IA and SWIFT PRIME, both studies used automated software (RAPID, iSchemaView, Menlo Park) to determine the ischemic core, and in DEFUSE 3, the penumbra volumes.[13] Either computed tomography (CT) perfusion or magnetic resonance imaging diffusion/perfusion were allowed based on recent data showing that with the use of appropriate thresholds and analysis techniques, CT perfusion is able estimate the ischemic core with accuracy that is comparable to magnetic resonance imaging.[14,15] Because of the requirement for small core volumes in extended time windows, the vast majority of patients enrolled in both DAWN and DEFUSE 3 were in the green slow growing core category. In fact, the majority of patients in these trials were enrolled at >10 hours and had core volumes of ≤10 mL—these patients had early growth rates of ≤1/mL hour before enrollment! For these patients, even a 2- to 3-hour delay between imaging and reperfusion would not be anticipated to lead to any consequential infarct growth. Because these patients had proximal middle cerebral artery or internal carotid artery occlusions, a very large volume of penumbral salvage would be anticipated if substantial or complete reperfusion is obtained. However, for the medical arm patients in these late window trials, very poor outcomes would be anticipated for 2 key reasons. (1) No intravenous tPA therapy was administered in >90% of these patients—therefore the ≈35% to 40% reperfusion rate seen in patients with favorable imaging profiles who are treated with tPA[9,10] did not occur, and patients who achieved early spontaneous reperfusion were excluded. (2) Eventually, the collateral circulation fails and infarcts evolve into the region of critical hypoperfusion.[4] Based on perfusion imaging, the volume of tissue at risk is typically substantial in patients with middle cerebral artery or internal carotid artery occlusions, even if good collaterals are present. Only a minority (probably <10%) of these patients have collaterals that are adequate to assure a favorable outcome in the absence of reperfusion. The bottom line is that the medical therapy arms patients in the late window trials had extremely low rates of good outcome, whereas the endovascular arms had favorable outcome rates that were comparable to the early window trials. Therefore, the absolute benefit was larger in the late window studies.

Paradox Deciphered

In summary, the critical factors that explain the paradox are (1) a substantial percentage of patients with large vessel intracranial occlusions have very slow growth of the ischemic core for up to 12 hours or longer; (2) the favorable collateral circulation that is responsible for keeping the

ischemic core size small eventually fails in most patients and infarct volumes ultimately increase; and (3) clinical outcomes in the control groups of the randomized trials are strongly influenced by whether or not tPA was administered. Therefore, late arriving patients with large vessel occlusions and small infarct core volumes can have extremely robust treatment effects.

Clinical Implications

The "time is brain" concept requires a 2018 revision that is more generous than the original and provides a reprieve for the fortunate patients who have favorable collaterals and slow infarct growth. However, because it is not possible to immediately determine the growth rate of the ischemic core, it remains critical to evaluate all stroke patients as urgently as possible. For those who arrive early with a large ischemic core lesion, randomized trials are needed to clarify whether thrombectomy is beneficial. Further research is also needed to clarify whether patients who are transferred within 6 hours of onset to comprehensive centers, with a CT angiography-documented large vessel occlusion and an eligible noncontrast CT, require repeat imaging at the thrombectomy site. The advantage of repeat imaging is that patients who have developed a very large infarct core, suffered hemorrhagic transformation, or experienced reperfusion while in transit, can be spared a resource-intensive invasive procedure. The disadvantage is that for patients with rapid growth rates, the additional time required for imaging may result in less salvageable tissue. Stroke patients in whom thrombectomy can be initiated within 6 to 24 hours should be screened with advanced imaging to determine whether they meet DEFUSE 3 or DAWN criteria for late window thrombectomy. Both late window studies required CT perfusion or DWI to assess the size of the ischemic core and, in DEFUSE 3, CT or magnetic resonance perfusion imaging to estimate the volume of penumbral tissue. Therefore, because access to acute magnetic resonance imaging remains limited, CT perfusion will be required to select late window stroke patients for thrombectomy at most hospitals. As more primary stroke centers begin to perform advanced imaging, these data should be rapidly shared with the comprehensive center to help optimize triage decisions.

Disclosures

Dr Albers has an equity interest in iSchemaView and is a consultant for iSchemaView and Medtronic.

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