DAWN of a New Era for Stroke Treatment: Implications of the DAWN Study for Acute Stroke Care and Stroke Systems of Care

Running Title: Alberts et al.; Implications of the DAWN Study

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Until recently, the selection of patients with large artery occlusion and ischemic stroke for reperfusion therapy was based on time criteria (typically within 6 hours) and basic imaging protocols (head CT, CT angiogram, ASPECTS score). The recently published DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) study has changed this paradigm by using a tissue-based selection criteria and a greatly expanded treatment time window (up to 24 hours). This is a transformational change in acute stroke therapy and has implications for many healthcare providers and EMS systems.

**Patient Selection Using Advanced Imaging**

Key to the selection of patients that may benefit from mechanical thrombectomy is identifying those with a relatively small area of core infarction. All DAWN patients had clinical and CTA evidence of a large artery occlusion (distal internal carotid or proximal middle cerebral artery) causing a significant neurologic deficit. Patients then had core size and salvageable areas determination using one of two modalities; CT perfusion (CTP) or MR diffusion. For both modalities, analysis of the size of the core was determined in an automated fashion utilizing the RAPID software package (iSchemaView, Inc). Enrollment was based on a combination of age, stroke severity, and core infarct size. Most patients (76%) had core infarct size determination using CTP. Patients with a favorable core:salvageable brain ratio were treated with mechanical thrombectomy (MT) using the TREVO stent-triever, or best medical therapy.

**DAWN Study Design and Results**

The study was stopped prematurely based on an interim analysis after 206 patients were enrolled. The proportion of patients with functional independence (defined as a modified Rankin score of 0-2 at 90 days) was 49% in the treatment arm vs. 13% in the medical arm, with an absolute risk
reduction in disability of 36% (95% CI 24-47, see table). This absolute 36% increase in good functional outcome translated into a number needed to treat of 2.8 to prevent severe disability. Patients treated within 12 hours of stroke onset had better outcomes compared to those treated 12-24 hours after stroke onset (see table). Rates of symptomatic ICH were similar (see table).\(^1\)

**Implications for Stroke Centers**

Based on the results of DAWN and the recently terminated DEFUSE3 studies (which had a similar design), RAPID imaging and MT must be made available to patients outside of large metropolitan areas, where Comprehensive Stroke Centers (CSCs) are largely concentrated. The network of approximately 1500 Primary Stroke Centers (PSCs) in the U.S. is a logical resource, since their geographic distribution is more diverse than CSCs, with many PSCs in suburban regions and even smaller cities.

Some studies suggest that up to a third of PSCs may offer MT, which could triple the number of stroke centers offering such therapy.\(^3\) PSCs offering MT (the Brain Attack Coalition designates them as enhanced PSCs [PSC-E]), may require additional staffing and infrastructure. This includes advanced imaging resources (i.e. RAPID), a MT suite with the needed support staff and supplies, physicians appropriately trained in endovascular MT, and possibly neuro-critical care in some areas. We estimate that the additional costs for RAPID software, combined with equipping and staffing an endovascular suite for MT could exceed $100,000-$150,000. The DRG for endovascular treatment of stroke is associated with reimbursements > $30,000 in most cases. Thus at high volume centers, the financial implications could be positive or neutral.

**Implications for Stroke Systems of Care**

EMS should perform field screening to identify patients likely to have a stroke caused by a large vessel occlusion.\(^4\) There are several scales being tested. Stroke systems must define and
delineate resources (EMS, transportation modalities, stroke centers, etc.) that span a region and can be organized to provide efficient identification, diversion, and transportation. Although providing MT services on a 24/7/365 basis would be preferable in terms of consistency of EMS diversion protocols, some PSC-Es in remote locations may not be able to achieve this. Data are currently insufficient to define minimum case volumes (by PSC-E or practitioner) that correlate with improved or optimal outcomes. Recent studies suggest that direct transfer of patients with severe strokes to a CSC may be a useful strategy for reducing treatment times and improving outcomes. However this may not be feasible in all regions due to logistical limitations.  

Regional authorities should analyze resources and design a system that optimally aligns and distributes resources to best serve their citizens. Allowable by-pass times for EMS to divert to a PSC-E or CSC should reflect the variable geography and logistical issues encountered in different regions of the U.S. Such times might vary between 15 minutes and 1 hour or more based on these local factors. It is unclear if mobile stroke units will be beneficial in such a system; there may be some benefit in rural areas with sparse resources and long transportation times/distances. Each system or region should establish protocols that are feasible based on these considerations, and track patient outcomes. Although a 24 hr treatment time window allows for some degree of flexibility, earlier therapy is still associated with better outcomes (see table).

**Conclusions**

The DAWN treatment paradigm is transformational for acute stroke care, and has significant implications for Stroke Centers and Stroke System of Care. Moving from a time-based selection perspective to a tissue-status based approach appears to improve the efficacy and safety of reperfusion therapy using MT. The expansion of treatment times to 24 hours has the potential to
benefit a significant proportion of stroke patients who may have been otherwise categorically denied this treatment.

Disclosures

None

Statistical analysis conducted by Drs. Alberts, Ollenschleger, and Nouh

Author Contributions

Dr. Alberts, concept, data analysis, draft manuscript, critical revisions
Dr. Ollenschleger, data analysis, interpretation of data, critical revisions
Dr. Nouh, draft manuscript, interpretation of data, critical revisions

References


### Table. DAWN Trial: Baseline Characteristics and Outcomes

<table>
<thead>
<tr>
<th>Presentation and Outcomes</th>
<th>Treatment Arm (n=107)</th>
<th>Control Arm (n=99)</th>
<th>Comment/Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time LKW (median hrs)</td>
<td>12.2</td>
<td>13.2</td>
<td>Range 6.1-23.5 MT; 6.5-23.9 medical</td>
</tr>
<tr>
<td>NIHSS (median)</td>
<td>17 (13-21)</td>
<td>17 (14-21)</td>
<td>Moderately severe strokes</td>
</tr>
<tr>
<td>Stroke Sx present upon awakening</td>
<td>64.5%</td>
<td>47.5%</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>mTICI score 2B or greater</td>
<td>84%</td>
<td>NA</td>
<td>High rates of reperfusion in treatment arm</td>
</tr>
<tr>
<td>mRS 0-2 at 90 days</td>
<td>49%</td>
<td>13%</td>
<td>Posterior probability of superiority &gt;0.999</td>
</tr>
<tr>
<td>6-12 h presentation</td>
<td>54%</td>
<td>20.0%</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>&gt;12-24 h presentation</td>
<td>44%</td>
<td>8%</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Stroke Mortality (90 days)</td>
<td>16.0%</td>
<td>18.0%</td>
<td>All-cause mortality 19% v 18%</td>
</tr>
<tr>
<td>Symptomatic ICH (24 hrs)</td>
<td>6%</td>
<td>3%</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Neurologic deterioration (24 hrs)</td>
<td>14%</td>
<td>26%</td>
<td>P = 0.04</td>
</tr>
</tbody>
</table>

LKW: time last known well  
NIHSS: modified NIH stroke scale  
mTICI: modified Thrombolysis in Cerebral Infarction scale  
mRS: modified Rankin score  
ICH: intracranial hemorrhage
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