Eligibility for Endovascular Trial Enrollment in the 6- to 24-Hour Time Window

Analysis of a Single Comprehensive Stroke Center

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Background and Purpose—The results of the DAWN trial (Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) support the benefit of endovascular therapy in patients presenting beyond the 6-hour time window with anterior circulation large vessel occlusions. The impact of these results with respect to additional number of eligible patients in clinical practice remains unknown.

Methods—A retrospective review of ischemic stroke admissions to a single DAWN trial-participating comprehensive stroke center was performed during the DAWN enrollment period (November 2014 to February 2017) to identify patients meeting criteria for DAWN and DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke-3) eligibility. Patients presenting beyond 6 hours were further investigated to clarify reasons for trial exclusion.

Results—Of the 2667 patients with acute ischemic stroke admitted within the study period, 30% (n=792) presented within the 6- to 24-hour time window, and 47% (n=1242) had a National Institutes of Health Stroke Scale ≥6. Further clinical trial-specific selection criteria were applied based on the presence of large vessel occlusion, baseline modified Rankin Scale score, core infarct, and perfusion imaging (when available). There were 45 patients who met all DAWN trial criteria and 47 to 58 patients who would meet DEFUSE-3 trial criteria. Thirty-three percent of DAWN-eligible patients are DEFUSE-3 ineligible.

Conclusions—Of all patients with acute ischemic stroke presenting to a single comprehensive stroke center, 1.7% of patients qualified for DAWN clinical trial enrollment with an additional 0.6% to 1% qualifying for the DEFUSE-3 trial. These data predict an increase in thrombectomy utilization with important implications for comprehensive stroke center resource optimization and stroke systems of care. **(*Stroke*. 2018;49:1015-1017. DOI: 10.1161/STROKEAHA.117.020273.)**

Key Words: humans ■ incidence ■ patient selection ■ retrospective studies ■ thrombectomy

Current guidelines set forth by the American Heart Association and European societies restrict class-IA recommendation to patients treated within the 6-hour time window.[1,2] The benefit of endovascular therapy in the extended time window was investigated in the DAWN trial (Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo)[2] and the DEFUSE-3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke-3). Whereas results of DAWN were published showing strong benefit of thrombectomy over medical therapy alone,[3] DEFUSE-3 was halted because of high probability of benefit in the treatment arm.[4] Extending treatment time windows has significant implications for triage, resource allocation, and maximizing patient benefit. In this study, we perform a single, comprehensive stroke center analysis to understand the incidence of patients who could benefit from intra-arterial therapy in the extended time window.

Materials and Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. With institutional review board approval, a retrospective analysis of all acute ischemic stroke (AIS) during DAWN trial enrollment period (November 2014 to February 2017) was performed at our comprehensive stroke center. We used the Get With The Guidelines database. Patients were then filtered for analysis based on DAWN and DEFUSE-3 enrollment criteria: last seen well to emergency department arrival time (DAWN, 6–24 hours; DEFUSE-3, 6–16 hours), National Institutes of Health Stroke Scale (NIHSS; DAWN, ≥10; DEFUSE-3, ≥6), presence of proximal

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Table. Algorithm to Identify DAWN- and DEFUSE-3–Eligible Trial Patients

Total AIS=2667		DAWN Trial			DEFUSE-3 Trial
LSW to arrival time (percentage of total=2667)	6–24 h	792 (30%)	6–16 h		451 (17%)
NIHSS score (percentage of total=2667)	≥10	890 (33%)	≥6		1242 (47%)
Patients meeting LSW to arrival time and NIHSS criteria (percentage of total=2667)		298 (11.2%)		285 (10.7%)	
Presence of proximal anterior large vessel occlusion (MCA-M1/ICAT/intracranial IC occlusion with or without extracranial IC occlusion)		155		133	
Mismatch criteria and baseline mRS score		mRS score, 0–1	Core ≤50 cc and presence of clinical-core mismatch*	mRS score, 0–2	Target mismatch profile on perfusion imaging†
		45		47–58	
Percentage of patients eligible for trial enrollment (percentage of total=2667), %		1.7		1.8–2.2	
Patients meeting DAWN and DEFUSE-3 criteria (percentage of total=2667)		30 (1.1%)			
Patients meeting DAWN or DEFUSE-3 criteria (percentage of total=2667)		73 (2.7%)			

AIS indicates acute ischemic stroke; DAWN, Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke-3; IC, internal carotid; ICAT, internal carotid artery terminus; LSW, last seen well; MCA-M1, middle cerebral artery segment 1; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Age ≥80 y, NIHSS score ≥10, and infarct volume <21 mL; age <80 y, NIHSS score ≥10, and infarct volume <31 mL; or NIHSS score ≥20 and infarct volume <51 mL.

†Ischemic core volume is <70 mL, mismatch ratio is ≥1.8, and mismatch volume is ≥15 mL.

anterior circulation large vessel occlusion in the intracranial internal carotid artery or middle cerebral artery (segment 1/M1), clinical-core mismatch (DAWN), clinical-imaging mismatch (DEFUSE-3), baseline modified Rankin Scale score (DAWN, 0–1; DEFUSE-3, 0–2), life expectancy of >6 months, and ability to obtain consent. DAWN and DEFUSE-3 inclusion and exclusion criteria have been reported previously.[3,5] Imaging-based selection for DEFUSE-3 criteria could not be assessed for 19% of patients who met all other DEFUSE-3 criteria because of lack of perfusion imaging or core measurement. We calculated the percentage of patients who were eligible for DEFUSE-3 in the imaging available group and extrapolated it to the imaging unavailable group. Hence, we were able to derive a range for the DEFUSE-3 trial eligibility population. Ischemic core was estimated using the automated software RAPID (iSchemaView, Menlo Park, CA).

Results

Two thousand six hundred sixty-seven patients were identified with a discharge diagnosis of AIS between November 2014 and February 2017. Patients presenting within the 6- to 16-hour time window comprised 17% of all patients, which increased to 30% when extending to 6- to 24-hour time window. Patients presenting with NIHSS score ≥10 comprised 33% of all patients, which increased to 47% when including NIHSS score 6 to 9. Fifty-two percent (n=155) of patients meeting DAWN trial time window (6–24 hours) and NIHSS criteria (≥10; n=298), 47% (n=133) of patients meeting DEFUSE-3 trial time window (6–16 hours) and NIHSS criteria (≥6; n=285), and 43% (n=174) of patients presenting at 6 to 24 hours and with NIHSS score ≥6 (n=407) had study-eligible large vessel occlusion. Further refinement based on baseline modified Rankin Scale score and presence of clinical-core mismatch identified a total of 45 patients (1.7% of total AIS, 2667) who met all DAWN trial criteria (Table). Excluding imaging criteria, 118 patients met all other DEFUSE-3 criteria. Appropriate imaging data were only available in 95 patients; of them, 49% met imaging criteria for DEFUSE-3. Extrapolation of this percentage to the remaining 23 patients (appropriate imaging unavailable but meet other DEFUSE-3 criteria) identified a potential 11 additional patients who would meet DEFUSE-3 criteria (47–58 patients; 1.8%–2.2% of total, 2667). Thirty (1.1%) patients met criteria for both DAWN and DEFUSE-3, and 73 (2.7%) patients met criteria for DAWN and DEFUSE-3. Fifteen (33%) of 45 DAWN-eligible patients are DEFUSE-3 ineligible. (Figure). Patients who were ≥80 years of age accounted for 31% of the DAWN-eligible cohort and 32% of the DEFUSE-3 cohort. Mode of presentation of stroke was classified as (DAWN versus DEFUSE-3) (1) wake up

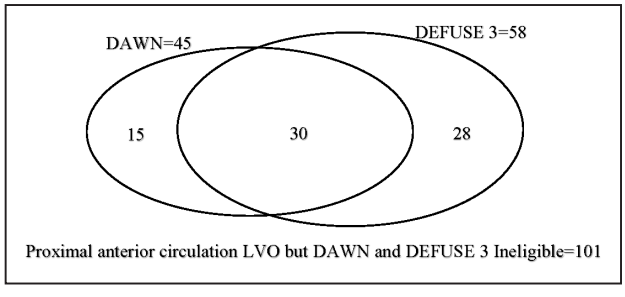

Figure. Venn diagram: acute ischemic stroke with large vessel occlusions (LVOs; 6–24 hours and National Institutes of Health Stroke Scale ≥6), n=174. DAWN indicates Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; and DEFUSE, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke-3.

(56% versus 53%), (2) unwitnessed (27% versus 23%), and (3) witnessed (17% versus 24%). Of the DAWN-eligible cohort (n=45), 23% were identified using computed tomographic perfusion imaging and 77% using magnetic resonance imaging. Eighty-two percent (n=37) of the DAWN-eligible patients were enrolled in the trial, and the remainder (n=7) did not consent.

Discussion

It has been reported that 10.5% of all patients with AIS presenting to a comprehensive stroke center within 6 hours of symptom onset qualify for endovascular therapy.[6] In this study, we find 1 in 3 patients with large vessel occlusion, and 5.7% of all patients with AIS presenting in the 6- to 24-hour time window qualify for endovascular therapy based on DAWN criteria. DEFUSE-3 trial also enrolled patients presenting beyond the 6-hour time window and included patients with lower NIHSS score, larger core infarct, and higher modified Rankin Scale score compared with DAWN. One third of DAWN-eligible patients are DEFUSE-3 ineligible. Expanding treatment based on both DAWN and DEFUSE-3 criteria would further broaden treatment eligibility to 9.2% of all patients presenting in the 6- to 24-hour time window. A third of eligible patients are elderly (>80 years), and nearly half present as wake-up strokes. Current guidelines limit class-IA recommendation to the 6-hour time window, and systems of care are currently being optimized to identify large vessel occlusion in these early time windows and deliver appropriate patients to endovascular-capable centers. Similarly, emergency medical services and referring facilities are currently attuned to an intravenous alteplase and intra-arterial time window; however, the extension of therapy ≤24 hours has significant implications for patient triage and hospital referrals.

Our study experiences several limitations inherent to a retrospective analysis of a single center. Imaging information was not available for a subset of DEFUSE-3–eligible patients. Given the general notion that stroke treatments are limited to early time windows, it is possible that many DAWN- and DEFUSE-3–eligible patients presenting initially to outside facilities were not considered treatment candidates, and so a subset of those patients may not have been referred to our facility, thereby underestimating the total number of potential late time window candidates. Also, because of the retrospective nature of our study, data on patients managed outside trial criteria were not available for comparison.

In summary, our analysis demonstrates that application of the DAWN and DEFUSE-3 enrollment criteria to an AIS population would impact 1.7% to 2.7% of total patients presenting to a comprehensive stroke center. These data have important implications for an anticipated rise in the number of thrombectomy-eligible patients and increased resource needs.

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Disclosures

Dr Jovin is a consultant at Stryker Neurovascular (principal investigator DAWN [Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo]-unpaid) and Blockade Medical (modest); is an advisory board member/investor at Anaconda (modest), FreeOx Biotech (modest), and Route92 (modest); and reports honoraria from Cerenovis (modest) and the Data Safety and Monitoring Board. The other authors report no conflicts.

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