Magnitude of Benefit of Endovascular Thrombectomy 6-24 Hours after Onset in Acute Ischemic Stroke Patients with Clinical-Core Mismatch

Disclosures

- JLS, APJ, DCH, AB, RFB, PB, DRY, RR, CC, RA, CAS, AEH, DSL, WSS: consulting fees and travel expenses for work advising on rigorous trial design and conduct
- RGN, TGJ: travel expenses only for work advising on rigorous trial design and conduct
Background: Patient Selection for Mechanical Thrombectomy

- Initial MT RCTs of highly effective devices generally time-focused patient selection
  - Pooled analysis - benefit rapidly decays, may be lost by 7.3 hours
  - National AHA+ESO guidelines endorsed only <6 hr window as IA evidence

- Physiologic, rather than purely time-based, selection may identify patients >6 hr from LKW who benefit
  - ~40% of AIS-LVO
    - Wake-up onset
    - Unclear onset time
    - Witness late onset, slow progressors unclear onset, w unclear onset time AIS-LVO
  - Clinical-Core Mismatch - substantial deficits but limited infarct

- DAWN tested this approach

Background: Indices of Treatment Benefit Magnitude

• DAWN
  • Primary endpoint: Utility-Weighted modified Rankin Scale

• Group-level, average benefit directly interpretable
  • Health-related utility, from 0% (death) to 100% (optimum health)
  • Average patient xx% improvement
Background: Indices of Treatment Benefit Magnitude

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  - Benefit per hundred (BPH): among 100 patients, how many benefit?
  - Number needed to treat (NNT): How many need to be treated for 1 to benefit?
Background: Indices of Treatment Benefit Magnitude

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- Current study to derive BPH and NNT values
  - Overall and in 6-12 and 12-24h time windows
Background: Indices of Treatment Benefit Magnitude

- DAWN primary results: ESOC (5/17), NEJM (11/17)
  - Primary endpoint: Utility-Weighted modified Rankin Scale, 5.5 vs 3.4
    - Abs diff 2.0 (95CrI 1.1-3.0), post p > 0.999
- Group-level, average benefit directly interpretable
  - Health-related utility, from 0% (death) to 100% (optimum health)
  - Average patient 20% improvement
- Patient-level indices of benefit also would be helpful, for patients, physicians, policy-makers
  - Benefit per hundred (BPH): among 100 patients, how many benefit?
  - Number needed to treat (NNT): How many need to be treated for 1 to benefit?
- Current study to derive BPH and NNT values
  - Overall and in 6-12 and 12-24h time windows
Methods: DAWN Design

To demonstrate superior functional outcomes at 90 days with Trevo plus medical management compared to medical management alone in appropriately selected patients treated six to 24 hours after last seen well

<table>
<thead>
<tr>
<th>Study design</th>
<th>Global, multi-center, adaptive, population enrichment, prospective, randomized, open, blinded endpoint (PROBE), controlled FDA IDE trial</th>
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</table>
| Patient population | • Acute ischemic stroke (AIS) with large vessel occlusion  
• Able to be randomized between six to 24 hours after time last known well  
• Clinical imaging mismatch (CIM) defined by age, core, and NIHSS |
| Target vessel | Intracranial ICA, M1 segment of the MCA |
| Randomization | 1:1 Trevo + medical management vs. medical management alone |
| Sites | Up to 50 sites worldwide (30 US and 20 international) |
| Sample size | 500 maximum subjects: 250 in the treatment arm and 250 in the control arm. Minimum sample size is 150 subjects. |
| Follow-up | 24 hours (-6/+24), day 5-7/discharge, day 30 (± 14), and day 90 (± 14) |
**Study Methods: Workflow**

**NCCT/DWI:**
- <1/3 MCA Territory

**CTA/MRA:**
- ICA-T and/or MCA-M1
  - (Tandem Occlusions Allowed)

**RAPID CTP/DWI CIM:**

A. ≥80 y/o:
   1. NIHSS ≥10 + core <21cc

B. <80 y/o:
   1. NIHSS ≥10 + core <31cc
   2. NIHSS ≥20 + core <51cc

**Randomization:**
- CIM subgroup
- ICA-T vs M1
- 6-12 vs 12-24h

**Informed Consent**

**Control**
- 90-day mRS
  - U-W mRS
  - mRS 0-2

**Thrombectomy**

**6-24h**

- Age ≥18
- NIHSS ≥10
- Pre-mRS 0-1
- TLSW to Randomization: 6-24h

**1:1**

- Pre-mRS 0-1
- 6-12 vs 12-24h
TRIAL STOPPED FOR AT FIRST INTERIM EFFICACY ANALYSIS:
OVERWHELMING EFFICACY IN 1ST 200 PATIENTS
DAWN Trial Utility-Weighted mRS

Utility weighted mRS

- Better captures health state transitions across the entire spectrum
- Patient-centered outcomes analysis

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<th>3</th>
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Minimal Clinically Important Difference (MCID)

- MCID for health-related utility is well-established: 0.3\(^1\)
- 5 transitions on the mRS are clinically valuable
  - 1 transition not clinically valuable, from mRS 6 to mRS 5

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\(^1\) Kaplan et al, Health Serv Res 1976;11:478-507; Kaplan, COPD 2005;2:91-7 (0.3 value is scaled to 0-10 range of UW-mRS version used in DAWN)
BPH and NNT Derivations

- Analyzed age, NIHSS, and core-adjusted 90d distributions
- For all dichotomized cutpoints of the mRS
  - NNT and BPH values by calculating inverse of absolute risk difference
- For improvements on the UW-mRS (= improvements by 1 or more levels across all steps of the 6 level mRS)
  - NNT and BPH values by automated joint outcome table resampling
    - R function “xsample” used to randomly sample values of the vector “x” from all possible joint outcome table solutions
    - Using the mirror algorithm, 3000 samples were taken from the large population of all possible solutions, without replacement.
    - Mean and range NNTB values were calculated for these random samples from all possible NNTB values under the constraints
Results
DAWN Treatment Group-Level Differences
Entire DAWN Cohort

mRS (6 level)
Stacked Bar Chart
DAWN Treatment Group-Level Differences
Entire DAWN Cohort

mRS (6 level)
Stacked Bar Chart

UW-mRS
Utility Staircase Plot
### mRS Outcomes – Entire DAWN Cohort

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For every 100 DAWN-like patients treated, thrombectomy yields improved disability-related quality of life in 50, including functional independence in 36.
DAWN Treatment Group-Level Differences
Time Window Cohorts

6-12 Hours

Thrombectomy (N=50)
- 14
- 22
- 18
- 10
- 6
- 30

Control (N=46)
- 7
- 7
- 6
- 11
- 37
- 33

>12-24 Hours

Thrombectomy (N=57)
- 5
- 23
- 16
- 16
- 19
- 21

Control (N=53)
- 4
- 21
- 32
- 40
mRS Outcomes – DAWN Time Window Cohorts

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DAWN Treatment Group-Level Differences

Time Window Cohorts

Thrombectomy (N=50):
- 6-12 Hours: 14, 22, 18, 10, 6, 30
- >12-24 Hours: 5, 23, 16, 16, 19, 21

Control (N=46):
- 6-12 Hours: 7, 7, 6, 11, 37, 33
- >12-24 Hours: 4, 21, 32, 40
DAWN Treatment Group-Level Differences
Time Window Cohorts

6-12 Hours

>12-24 Hours
DAWN Treatment Group-Level Differences

Time Window Cohorts

6-12 Hours

Control (N=46)
- Thrombectomy (N=50)

>12-24 Hours

Control (N=53)
- Thrombectomy (N=57)
Discussion: Comparison with Other Thrombectomy Trials

Disability-Related QoL (UW-mRS)

Level of Disability (mRS shift analysis)

Benefit Per Hundred* (Shift+Fxn Ind)

*In comparative analyses, BPH values were calculated using the algorithmic min-max joint outcome table method (rather than the multiple resampling joint outcome table method)
Discussion: Comparison with Other Thrombectomy Trials – 1A

Disability-Related QoL (UW-mRS)

Level of Disability (mRS shift analysis)

Benefit Per Hundred* (Shift+Fxnl Ind)

DAWN

HERMES 2H

*In comparative analyses, BPH values were calculated using the algorithmic min-max joint outcome table method (rather than the multiple resampling joint outcome table method)
Discussion: Comparison with Other Thrombectomy Trials – 1B

Disability-Related QoL (UW-mRS)

Level of Disability (mRS shift analysis)

Benefit Per Hundred* (Shift+Fxn Ind)

DAWN

HERMES 5H

*In comparative analyses, BPH values were calculated using the algorithmic min-max joint outcome table method (rather than the multiple resampling joint outcome table method)
Discussion: Comparison with Other Thrombectomy Trials - 2

Disability-Related QoL (UW-mRS)

Level of Disability (mRS shift analysis)

Benefit Per Hundred* (Shift+Fxn Ind)

*In comparative analyses, BPH values were calculated using the algorithmic min-max joint outcome table method (rather than the multiple resampling joint outcome table method).
Conclusions

• Endovascular thrombectomy with the Trevo device at 6-24h in patients with clinical-core mismatch confers benefit of substantial magnitude, improving 90 day disability levels in one-half of patients, including conferring functional independence in one-third.

• Benefit is substantial in both the 6-12h and >12-24h time windows, with about half of patients benefitting in both periods. But earlier patients do better in both the thrombectomy and control groups.

• The proportion of patients benefitting in DAWN is similar in magnitude to that observed in broadly screened patients selected for treatment at 2h, and substantially higher than that seen for broadly selected patients at 5h.
Enrolling Centers

**North America**
1. Abington Memorial, PA
2. Baptist Jacksonville, FL
3. Buffalo, NY
4. Capital Health Trenton, NJ
5. Christiana Delaware, DE
6. CPMC San Francisco, CA
7. Erlanger, Chattanooga, TN
8. Florida Hospital, FL
9. Grady Atlanta, GA
10. JFK, Edison, NJ
11. Kaiser LA
12. Kennestone, Marietta GA
13. KUMC Kansas City, KA
14. Lexington Memorial, KY
15. Riverside, OH
16. Rush, IL
17. St. Joseph Mercy MI
18. Texas Stroke Institute TX
19. Toronto Western, ON
20. UCLA, CA

21. UH Cleveland, OH
22. University of Miami, FL
23. UPMC, PA
24. Valley Baptist, TX

**Europe**
26. Bellvitge Barcelona
27. Germans Trias Barcelona
28. Gui de Chauliac Montpellier
29. Hospital Purpan Toulouse
30. Hospital Clinic Barcelona
31. Vall d’Hebron Barcelona

**Australia**
32. Royal Melbourne Hospital
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STRYKER NEUROVASCULAR DAWN CLINICAL TEAM

• Alice Lin, CRA, Lead Clinical Research Associate
• Patricia Morgan, BSN, RN, Lead Clinical Research Associate
• Ryan Shields, MSc, Sr. Manager, Data Management and Biostatistics
• Christine Toruno MSc, DAWN Project Manager
Thank you
to all DAWN investigators, patients and families