Intra-arterial Stroke Therapy: 2018 Update

Expanding the Treatment Window

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Medical Director
Disclosures

• Enrolling investigator
  • Stryker Neurovascular (DAWN trial)
Most common large vessel blockages

“MCA”

“ICA”
Large amount of brain at risk of damage

Large vessel occlusion (LVO)
Penumbra (at risk)

Infarct (irreversibly damaged)
Opening large vessel occlusions

**STENTRIEVER (early 2012)**

3RD GENERATION

Engage the thrombus with stent retrieve deployment, which also temporarily restores flow across the occlusion. Proximal balloon inflation allows device retrieval into the guide while minimizing the risk of emboli.
Era of intra-arterial stroke therapy

IN THE NEW ENGLAND JOURNAL OF MEDICINE

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke


ABSTRACT

In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion, intraarterial treatment is highly effective for emergency revascularization. However, proof of a beneficial effect on functional outcome is lacking.

METHODS

We randomly assigned eligible patients to either intraarterial treatment plus usual care or usual care alone. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that was confirmed on neuroimaging and that could be treated intraarterially within 6 hours after symptom onset. The primary outcome was the modified Rankin scale score at 90 days; this categoric scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). The trial was registered with ClinicalTrials.gov as NCT01252397.

RESULTS

We enrolled 706 patients at 36 medical centers in the Netherlands (378 assigned to intraarterial treatment and 328 to usual care alone). The mean age was 67 years (range, 20 to 96), and 444 patients (63%) were treated with intraarterial stenting after carotid occlusion. Retreatment stents were used in 196 of the 233 patients (84%) assigned to intraarterial treatment. The adjusted common odds ratio was 1.67 (95% confidence interval, 1.21 to 2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.7 to 21.3) in the rate of functional independence (modified Rankin score, 0 to 2) in favor of the intervention (52.9% vs. 39.4%). There were no significant differences in mortality or the occurrence of symptomatic intracranial hemorrhage.

CONCLUSIONS

In patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe. (Funded by the Dutch Heart Foundation and others; NCT01252397; Current Controlled Trials number, ISRCTN38887874.)

The authors’ full names, academic de- tails, and affiliations are listed in the Ap- pendix. Authors’ declared no con- flicts. D.E.J. is supported by a grant from the University Medical Center Groningen, VU University Medical Center Amsterdam, NOS, Maastricht, Netherlands, and Genentech, San Francisco, California. B. Van der Lugt, Institute for Research in Tuberculosis, Seoul, South Korea, and Maastricht, Netherlands.

The authors declare no con- flicts. H. Leurink, doctoral fellow, and S. M. T. van der Vleuten, research fellow, are members of the Steering Committee of the Nery Stent Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands. For tables and figures, see the full text on NEJM.org.

The new standard of care

NNT to get one patient to independence

4-7 pts

• AHA/ASA Class I, LOE A recommendation in support of intra-arterial therapy (thrombectomy) within 6 hours of stroke onset
Time is Brain

Increasing benefit of thrombectomy

Increasing time to treatment
Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (Class I; Level of Evidence A). (New recommendation):

a. Prestroke mRS score 0 to 1,
b. Acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
c. Causative occlusion of the ICA or proximal MCA (M1),
d. Age ≥18 years,
e. NIHSS score of ≥6,
f. ASPECTS of ≥6, and
g. Treatment can be initiated (groin puncture) within 6 hours of symptom onset.
What Don’t We Know

• **Class IIb recommendations for Endovascular Therapy** *(2015 Update to the AHA Guidelines)*
  • Extended time window (>6 hours)
  • Large infarcts (ASPECTS <6)
  • Mild strokes (NIHSS <6)
  • Distal (M2/M3, ACA) and posterior circulation occlusions
  • Pediatric (<18 yrs old)
  • Various procedural approaches (including aspiration catheters, anesthetic management)
  • Appropriate triage mechanisms (including bypass of PSCs for high suspicion LVO patients)
What Don’t We Know

• Class IIb recommendations for Endovascular Therapy (2015 Update to the AHA Guidelines)
  • Extended time window (>6 hours) → DAWN & DEFUSE 3 trials
  • Large infarcts (ASPECTS <6)
  • Mild strokes (NIHSS <6)
  • Distal (M2/M3, ACA) and posterior circulation occlusions
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DAWN in Full Daylight

DWI or CT Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Reintervention with Trevo

Tudor G. Jovin MD & Raul G. Nogueira MD on behalf of the DAWN investigators
**Study Objective**

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.

**Study Design**

<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>
</tr>
</thead>
</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**

**6-24h**

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

**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:
  2. NIHSS ≥10 + core <31cc
  3. NIHSS ≥20 + core <51cc

**Informed Consent**

1:1 Randomization:
- CIM subgroup
- ICA-T vs M1
- 6-12 vs 12-24h

**Control**

- U-W mRS
- mRS 0-2

**90-day mRS**

**Thrombectomy**
# Study endpoints

<table>
<thead>
<tr>
<th><strong>Primary endpoint</strong></th>
<th><strong>90-day disability assessed by the modified Rankin scale (mRS)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Assessed via Utility-Weighted mRS</td>
</tr>
<tr>
<td></td>
<td>• Nested <strong>Dichotomous mRS 0-2</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Secondary endpoints</strong></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• “Early response” at day 5-7/discharge, defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1</td>
</tr>
<tr>
<td></td>
<td>• All cause mortality rates</td>
</tr>
<tr>
<td></td>
<td>• Median final infarct size at 24 (-6/+24) hours from randomization</td>
</tr>
<tr>
<td></td>
<td>• Revascularization rates at 24 (-6/+24) hours from randomization</td>
</tr>
<tr>
<td></td>
<td>• Treatment arm: reperfusion rates post device and post procedure by angiography core lab measurement of modified TICI &gt; 2b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Primary safety endpoint</strong></th>
<th>Stroke related mortality at 90 days</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Secondary safety endpoint</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization</td>
</tr>
<tr>
<td></td>
<td>• Incidence of neurological deterioration from baseline NIHSS score through day 5-7/discharge</td>
</tr>
<tr>
<td></td>
<td>• Incidence of procedure-related and device-related serious adverse events through 24 (-6/+24) hours post randomization</td>
</tr>
</tbody>
</table>
Modified Rankin Score (Post Stroke Disability)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Living independently
Results

CBF (<30%) volume: 2.0 ml
Perfusion (Tmax>6.0s) volume: 100.0 ml
Mismatch volume: 98.0 ml
Mismatch ratio: 50.0
This image is not intended for primary diagnosis
Randomization and follow-up

Randomized (n=206)

Stratification by clinical core mismatch, time, and occlusion location

Trevo + MM N=107

Final FU available
106 90-day complete
1 withdrew after 30 day visit*

MM N=99

Final FU available
96 90-day complete
2 LTFU after 30 days*
1 withdrew after 30 day visit*

* 30 day mRS carried forward in 4 pts
100% follow-up to 30 days
### Baseline imaging characteristics

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm N=107</th>
<th>Control arm N=99</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying infarct volume by site RAPID (median, [IQR])</td>
<td>8.0 [2.0-18.0]</td>
<td>8.8 [3.0-18.1]</td>
<td>0.99</td>
</tr>
<tr>
<td>Infarct volume by core lab (median, [IQR])</td>
<td>9.0 [0.0, 19.0]</td>
<td>11.0 [0.0-19.0]</td>
<td>0.78</td>
</tr>
<tr>
<td>Patients with baseline MRI (%)*</td>
<td>43.0%</td>
<td>37.8%</td>
<td>0.48</td>
</tr>
<tr>
<td>Patients with baseline CT/CTA/CTP(%)*</td>
<td>76.6%</td>
<td>76.5%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Entire MCA territory is 300 ml

*Patients may have both CTP and MRI

Patients had great collaterals!
## Patient presentation

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm N=107</th>
<th>Control arm N=99</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time since time last seen well to randomization (hrs)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>13.4 ± 4.1</td>
<td>13.0 ± 4.5</td>
<td>0.53</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>12.2 (10.2, 16.0)</td>
<td>13.2 (9.4, 15.8)</td>
<td></td>
</tr>
<tr>
<td>Range (min, max)</td>
<td>(6.1, 23.5)</td>
<td>(6.4, 23.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke sub-population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake up stroke</td>
<td>64.5%</td>
<td>47.5%</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Witnessed stroke</td>
<td>10.3%</td>
<td>14.1%</td>
<td>0.52</td>
</tr>
<tr>
<td>Un-witnessed stroke</td>
<td>25.2%</td>
<td>38.4%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

~85-90% of patients had unknown time of onset
# Procedural characteristics and outcomes

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=107</td>
</tr>
<tr>
<td><strong>Procedure duration (minutes) (median IQR)</strong></td>
<td>56.0 [33.0-90.0]</td>
</tr>
<tr>
<td><strong>Total number of Trevo device passes (median IQR)</strong></td>
<td>2.0 [1.0-3.0]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=107</td>
</tr>
<tr>
<td><strong>Core lab adjudicated TICI</strong></td>
<td></td>
</tr>
<tr>
<td>Post procedure mTICI ≥ 2B</td>
<td>84.0%</td>
</tr>
<tr>
<td>Post procedure oTICI ≥ 2B*</td>
<td>72.6%</td>
</tr>
<tr>
<td>Post procedure TICI 3</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

*Protocol advised to stop after oTICI 2b achieved

**Restoration of blood flow to >50% of the ischemic brain**
Interventional treatment was as safe as medical management.
Primary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Trevo</th>
<th>MM</th>
<th>Treatment benefit (95% CI)</th>
<th>Bayesian probability of superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 90 weighted mRS</td>
<td>5.5 ± 3.8</td>
<td>3.4 ± 3.1</td>
<td>2.1 (1.20, 3.12)</td>
<td>&gt;0.9999*</td>
</tr>
<tr>
<td>Day 90 mRS (0-2)</td>
<td>48.6%</td>
<td>13.1%</td>
<td>35.5% (23.9%, 47.0%)</td>
<td>&gt;0.9999*</td>
</tr>
</tbody>
</table>

NNT for 90-day functional independence = 2.8

*Similar to p<0.0001
Primary outcome

Probability of superiority >0.9999

NNT for any lower disability = 2.0
90 Day mRS 0-2 by TLSW to Randomization

<table>
<thead>
<tr>
<th></th>
<th>Trevo</th>
<th>MM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12h</td>
<td>55.1%</td>
<td>20.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12-24h</td>
<td>43.1%</td>
<td>7.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Treatment benefit seen up to 24 hrs
Secondary effectiveness endpoints

**24 hour revascularization rates**

- Trevo: 76.6%
- MM: 38.4%

Relative improvement: 100%

P < 0.001

**All cause mortality**

- Trevo: 18.7%
- MM: 18.2%

P = 1.0

No increased mortality
Conclusions

- Thrombectomy with Trevo in DAWN-eligible patients is associated with improvement in clinical outcomes across the entire range of utility weighted mRS and with higher rates of functional independence (mRS 0-2) compared to standard medical therapy (48.6% vs 13.1%, probability of superiority >0.999, NNT = 2.8)

- **For every 100 patients treated with endovascular therapy, 49 will have a less disabled outcome as a result of treatment, including 36 who will be functionally independent**

- The treatment effect size in DAWN is the highest out of any stroke trials to date and suggests that the presence of Clinical-Core Mismatch is a critical predictor of treatment effect independent of time to presentation

- **Treatment effect persisted throughout 24 hours from TLKW; however, earlier treated patients do better**

- Thrombectomy with the Trevo device in patients presenting beyond 6 hours of TLSW had comparable safety profile to thrombectomy performed within 6 hours
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
## Extended Window Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>DAWN</th>
<th>DEFUSE 3</th>
<th>POSITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Inclusion Criteria</strong></td>
<td>NIHSS ≥ 10, Age ≥ 18, Clinical imaging mismatch:</td>
<td>NIHSS ≥ 6, Age 18-90, Perfusion imaging mismatch:</td>
<td>NIHSS ≥ 8, Age ≥ 18, ASPECTS ≥ 7</td>
</tr>
<tr>
<td></td>
<td>A. ≥80 y/o:</td>
<td>ischemic core &lt; 70 mL, perfusion mismatch ratio ≥ 1.8 and at least 15 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. NIHSS ≥10 + core &lt;21cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. &lt;80 y/o:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. NIHSS ≥10 + core &lt;31cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. NIHSS ≥20 + core &lt;51cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interventional Arm</strong></td>
<td>Endovascular thrombectomy with Trevo</td>
<td>Intra-arterial therapy</td>
<td>Intra-arterial therapy</td>
</tr>
<tr>
<td><strong>Control Arm</strong></td>
<td>Best medical management (+/- IV t-PA)</td>
<td>Best medical management (+/- IV t-PA)</td>
<td>Best medical management (+/- IV t-PA)</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>206 (I:107, C:99)</td>
<td>182 (I:92, C:90)</td>
<td></td>
</tr>
<tr>
<td><strong>Time window for Intervention</strong></td>
<td>6 – 24 hours</td>
<td>6 – 16 hours</td>
<td>6 – 12 hours</td>
</tr>
</tbody>
</table>
DEFUSE 3: Perfusion mismatch

Small infarct with larger volume of “at risk” tissue

Volume of Ischemic Core, 23 ml
Volume of Perfusion Lesion, 128 ml

Mismatch volume, 105 ml
Mismatch ratio, 5.6
DEFUSE 3: Primary outcome

- **Functional independence at 90 days:** 45% IAT vs. 17% control (P<0.001)
- **90-day mortality:** 14% IAT vs. 26% control (P=0.05)
- **sICH:** 7% IAT vs. 4% control (P=0.75)
The Late Window Paradox

• If time is brain, then
  • Why are outcomes so good in patients treated with stroke intervention beyond 6 and up to 24 hours after last known normal?
  • And why is the treatment benefit so large?
Penumbra (at risk)

Infarct (irreversibly damaged)
Larger infarct size at presentation

**Imaging** identifies patients with **good collaterals** who will benefit at extended time windows

The Late Window Paradox

• If time is brain, then
  • Why are outcomes so good in patients treated with stroke intervention beyond 6 and up to 24 hours after last known normal?
    • Imaging selection identifies patients with good collaterals
  • And why is the treatment benefit so large?
    • The control groups in DAWN and DEFUSE 3 were ineligible for IV tPA, and did worse than the control groups in the early-window trials
Stroke Case

Patient: JB
Info/History

• 52 yo male LSN at 22:45
• Left sided weakness, facial droop and slurred speech. NIHSS 10.
• Received IV tPA and found to have right internal carotid artery (ICA) thrombus.
• TSI consulted
Code stroke noncontrast CT Head showing no bleed and “hyperdense sign” (arrow) in right middle cerebral artery (MCA), indicating a possible large artery clot.
CT Angiogram showing vessel occlusion of the right ICA
MRI indicating already damaged area. Area between yellow arrows is presumed tissue at risk.
AP Angiogram showing Distal ICA occlusion and no filling of the right MCA or ACA.

Poor filling of the ICA due to high grade stenosis lower down requiring Emergent Angioplasty
After angioplasty, able to get catheters beyond the stenosis to remove clot from the distal right ICA.
Follow up

• Next day NIHSS 0
• Patient was discharged home
• Doing well, and enjoying life with wife and young children
DAWN-like Case

01 47 year old man with remote history of Hodgkin's Lymphoma

02 LKN at 0700 by wife

03 Wife returns at 1440, calls EMS

04 EMS performs severity scale, transports to CSC, arrives at 1508
DAWN-like Case

Arrival NIHSS 18

CT head (ASPECTS 8), CTA – right MCA occlusion

IR Suite arrival at 1525
DAWN-like Case

- recanalization at 1552

- Immediate post-procedure NIHSS 6
Implications of DAWN and DEFUSE 3

More patients eligible for Thrombectomy treatment.
Greater need for field triaging for CSC evaluation.
Hospitals will need more resources (Staffing/call teams/Physicians/equipment)
More stroke patients going home.
BREAKING NEWS!
• **NEW**: Mechanical thrombectomy is now recommended in LVO patients 6-16 hours from time last known normal and who meet DAWN and DEFUSE3 criteria. **Class 1, level A**
NEW: In patients presenting 16-24 hours from last know normal and who meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable Class 2a, level B-R.

The reason for this difference in the strength of recommendation is that only one RCT (DAWN) assessed this group of late-window patients; in general, Class 1, level A recommendations requires multiple RCTs.
NEW: In patient presenting between 6-24 hours of last known normal, obtaining CT perfusion, diffusion weighted MRI or MRI perfusion is recommended to aid in patient selection for MT, but only when imaging and other eligibility criteria from RCTs showing benefit are strictly applied. Class 1, level A.
• UPDATED: Waiting for IV-tPA to fail in patients being considered for mechanical thrombectomy was upgraded to recommendation level 3: harmful.
Improving Stroke Care in North Texas

- **MR CLEAN**: 1st trial to demonstrate the benefit of mechanical stroke intervention (2015)
- **DAWN**: 1st trial to expand the time window for stroke intervention to 24 hours (2017)
- **ARISE II**: Established the reperfusion benefit of the new EmboTrap device (2018)