Dawn to Defuse 3

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Disclosures

• None
2013

- IMS 3
  - 656 patients
  - IV tPA 3 hours vs IV tPA plus intervention

- mRS (0-2)
  - 40.8% Intervention
  - 38.7% IV tPA
2013/ 2014

- Cases for last 11 years.
2013 / 2014

- Cases for last 11 years.
Trials 2015

- **MR CLEAN** *(stent retriever /aspiration)*
  - 500 patients, 16 centers in Netherlands
  - 6 hours onset
  - MCA, ACA
  - CTA, MRA or angiography
  - NIHSS 2 or more
  - IV tPA, Intervention, or both
  - mRS 0-2 32.6% in Intervention Group
    - 19.1% in Control Group
Trials 2015

• EXTEND-IA
  • 100 patients (suspended after 70 patients)
  • IV tPA within 4.5 hours
  • Interventional (groin puncture) 6 hours
  • CTA with ICA or MCA occlusion
  • CT Perfusion with RAPID software

• mRS 0-2
  • 71% Interventional Group
  • 40% Control Group
Trials 2015

- **SWIFT-PRIME**
  - 196 Patients
  - Up to 6 hours
  - Small core infarct (ASPECTS score 6-10) CT Scan
  - ICA or M1 occlusion
  - **Perfusion** Imaging

- mRS 0-2
  - 60.2% Interventional Group
  - 35.5% Control Group
Trials 2015

- ESCAPE
  - 500 Patients (stopped 316 patients)
  - Up to 12 hours
  - Small core infarct (ASPECTS score 6-10) CT Scan
  - MCA occlusion
  - Good Collaterals
  - IV tPA was given 73% control arm, 79% Interventional arm
  - mRS 0-2
    - 53% Interventional Group
    - 29.3% Control Group
Problem(s)

- Patient presents with NIHSS 12
- Last seen normal 15 hours ago
- Head CT is Normal - No signs of Stroke
- What do we do ??
  
  - Perfusion CT/MRI Brain
  - If there is ischemia – Do you take to lab ?
  - Are you sure - Need DATA (Y/N, subgroups ...)
Everyone is Different

Rocha M, Stroke 2017
Clinical Question

- In patients with proximal internal carotid (ICA) or middle cerebral artery (MCA) occlusion with likely salvageable ischemic brain tissue, does thrombectomy, at 6-16 hours post ischemic stroke, in addition to medical therapy, compared to medical therapy alone, improve functional outcome at 90 days?

DEFUSE 3

- DEFUSE 3 trial examines the window between 6 and 16 hours using CT perfusion to select candidates.
DEFUSE 3

- Randomized, multi-centre trial, 1:1 randomisation, Web based randomisation software, that maintained allocation concealment
- Un-blinded due to invasive nature of experimental group
- Outcomes assessed in person, or by telephone if in-person visit was not feasible
- Study included a pre-determined analysis of those eligible for the DAWN trial
- All patients received CT perfusion or MRI with diffusion imaging
- Perfusion/diffusion imaging measuring infarct and ischemic size were calculated using RAPID software
- Power:
  a. To achieve a 90% power at an alpha of 5% a total of 476 patients were to be enrolled to detect a standardised effect of 0.36 for the reduction in modified Rankin scale
- Terminated early due to efficacy following an unplanned interim analysis following publication of the DAWN study
DEFUSE 3

- 38 hospitals in the US
- Data collected: May 2016- May 2017
- Inclusion criteria:
  - Age 18-90 years
  - NIHSS >=6
  - Likely salvageable ischemic brain tissue
    - Occlusion of proximal MCA-M1 or ICA on CT/MR angiography
    - Infarct volume < 70 ml on imaging
    - Ischemic tissue:Infarct volume ratio >= 1.8
    - Absolute volume of potentially reversible ischemia (penumbra) >=15 ml
  - Able to initiate endovascular therapy between 6-16 hours after time that last known to be well
  - Minimal pre-existing disability (Modified Rankin Scale, mRS, 0-2)
DEFUSE 3

- 182 patients randomised, 3 patients lost to follow up
- Groups were comparable at baseline (endovascular vs medical)
  - Age: 70 vs 71
  - Sex (F): 50% vs 51%
  - Median NIHSS: 16 vs 16
  - Witnessed stroke: 34% vs 39%
  - Wake-up stroke: 53% vs 47%
  - Pre-treated with tPA: 11% vs 9%
  - Infarct volume (ml): 9.4 vs 10.1
  - Volume of perfusion lesion (ml): 114.7 vs 116.1
  - Occlusion sites
    - ICA: 35% vs 40%
    - MCA: 65% vs 60%
  - Median time from stroke onset to qualifying imaging:
    10:29hrs vs. 9:55hrs
  - Median time to reperfusion 12.05 hours
DEFUSE 3

Intervention

- Thrombectomy plus medical therapy
  - Three devices approved for intervention: Trevo, Solitaire, and Penumbra devices
  - Angioplasty +/- stenting allowed as required
  - Femoral puncture to occur within 90 minutes of qualifying imaging (median time 59 min)
  - Intra-arterial tPA not allowed
- Medical therapy as per control group

Control

- Medical therapy:
  - Aspirin 325 mg on day 1, then 81-325mg mg on days 2-5
  - If tPA given prior to enrollment as per AHA guidelines (up to 4.5 hours post stroke onset) then sites post tPA pathway followed for medical treatment
DEFUSE 3

Outcome

- Functional independence (Modified Rankin 0-2) at 90 days – significantly increased with endovascular therapy
  - 45% vs 17%, OR 2.67 (95% C.I. 1.6-4.48), p<0.001
  - Number needed to treat (NNT) 4
  - Death at 90 days – no significant difference
  - 14% vs. 26%, OR 0.55 (95% C.I. 0.3-1.02), p=0.05
- Symptomatic intracranial haemorrhage – no significant difference
  - 7% vs. 4%, p=0.75
- Imaging outcomes, comparing endovascular vs. control group
  - No significant difference in:
    - Infarct volume at 24 hrs
      - 35ml vs. 41ml, p=0.19
    - Infarct growth at 24 hours
      - 23ml vs. 33ml, p=0.08
  - Significant increase in:
    - Re-perfusion >90% at 24 hrs in endovascular group
      - 79% vs. 18%, p<0.001, NNT 2
    - Complete recanalisation at 24 hrs in endovascular group
      - 78% vs. 18%, p<0.001, NNT 2
DEFUSE 3

The Bottom Line

- In patients with large vessel strokes with favourable ischemic core to penumbra ratios, endovascular therapy at 6-16 hours post stroke onset in addition to medical therapy, improved functional neurological outcome at 90 days, compared with medical therapy alone.
Clinical Question

- In patients who are 6-24 hours post acute stroke, and have a mismatch between clinical deficit and infarct, does thrombectomy plus standard medical care, compared to standard medical care alone, improve functional outcomes at 90 days?
DAWN

Setting
- 26 centres who performed at least 40 thrombectomy cases annually in: USA, Canada, Europe and Australia
- 206 patients enrolled (107 intervention, 99 control)
- Sept 2014 to Feb 2017

Population
- Inclusion criteria:
  - Age >= 18
  - Acute ischaemic stroke
  - Failed IV t-PA or treatment with IV t-PA contraindicated
  - Last known to be normal 6-24 hours previously
  - Baseline modified Rankin Scale (mRS) of 0 or 1
  - Occlusion of ICA and/or first segment MCA
  - Mismatch between severity of clinical deficit and infarct volume
  - Group A: > 80 yrs, NIHSS 10+, infarct volume < 21 ml
  - Group B: < 80 yrs, NIHSS 10+, infarct volume < 31 ml
  - Group C: < 80 yrs, NIHSS 20+, infarct volume 31-51 ml
DAWN 2018

- 206 patients
- Median age 70 yo    Gender Equal
- Median NIHSS 17.    Median infarct volume 7.6 ml
- Site Occlusion: ICA and/or MCA
- Time of Onset: 6-12 hours (55%) or 12-24 hours (43%)
DAWN 2018

- 206 patients
- Median age 70 yo, Gender Equal
- Median NIHSS 17, Median infarct volume 7.6 ml
- Site Occlusion: ICA and/or MCA
- Time of Onset: 6-12 hours (55%) or 12-24 hours (43%)
No significant difference in:

- 107 randomised to intervention group and 99 randomised to control group
- Age (yr): 69.4 vs. 70.7
- Age > 80: 23% vs. 29%
- Male sex: 39% vs. 52%
- Diabetes mellitus: 24% vs. 31%
- Prior ischemic stroke or TIA: 11% vs. 11%
- Median NIHSS: 17 vs. 17
- Infarct volume (ml): 7.6 vs. 8.9
- Occlusion site:
  - Intracranial ICA: 21% vs. 19%
  - M1 MCA: 78% vs. 78%
  - M2 MCA: 2% vs 3%
- Type of stroke
  - Unwitnessed stroke 27% vs. 38%
  - Witnessed stroke 10% vs. 14%
- Time from last well to randomisation: 12.2 hr vs. 13.3 hr
- Time of Onset: 6-12 hours (55%) or 12-24 hours (43%)
DAWN 2018

Significant difference in rates of:
- Atrial fibrillation: 40% vs. 24%, p=0.01
- Treatment with IV alteplase: 5% vs. 13%, p=0.04
- Wake up stroke: 63% vs. 47%, p=0.03

Intervention
- Mechanical thrombectomy with the Trevo device plus standard medical therapy
  - Use of rescue devices not permitted
  - Stenting of cervical ICA at time of thrombectomy not permitted
  - Thrombectomy performed in 105 of 107 patients
  - 3 of these patients underwent treatment with alternative endovascular reperfusion device after initial treatment with the Trevo device failed
  - BP control was used in post thrombectomy patients (SBP<140) to prevent ICH

Control
- Standard medical therapy only
DAWN 2018

Outcome

- Functional independence at 90 days (mRS 0-2)
  - 49% vs 13%
  - Absolute difference 36% (95% C.I. 24-47)
  - Adjusted difference 33% (95% CI 24-44)
  - pp superiority >0.999
  - NNT 3, fragility index of 22 patients

Authors’ Conclusions

- In patients with intracranial internal carotid artery or proximal MCA strokes who had mismatch of clinical symptoms vs infarct volumes and who were last seen normal 6-24 hours prior, thrombectomy is superior with regard to functional independence and disability at 90 days.
## DAWN Vs. DEFUSE3 Key Inclusion and population Differences

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<thead>
<tr>
<th></th>
<th>DAWN</th>
<th>DEFUSE-3</th>
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<tbody>
<tr>
<td>enrollment NIHSS</td>
<td>&gt;10</td>
<td>&gt;=6</td>
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<tr>
<td>Age</td>
<td>&gt;18</td>
<td>18-90</td>
</tr>
<tr>
<td>Infarct Size</td>
<td>Stratified, max 51ml</td>
<td>&lt;70 ml</td>
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<tr>
<td>Imaging Inclusion</td>
<td>Mismatch between severity clinical deficit and infarct volume</td>
<td>Ischemia to penumbra ratio</td>
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<tr>
<td>Time inclusion (hrs post last seen normal)</td>
<td>6-24</td>
<td>6-16</td>
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<tr>
<td>Device</td>
<td>Trevo</td>
<td>Trevo, Solitaire, penumbra</td>
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<tr>
<td>Actual AVG NIHSS</td>
<td>17</td>
<td>16</td>
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<tr>
<td>Study closure</td>
<td>Early-met efficacy</td>
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## DAWN Vs. DEFUSE3 Key Results Differences

<table>
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<tr>
<th></th>
<th>DAWN</th>
<th>DEFUSE-3</th>
<th>NNT</th>
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<tbody>
<tr>
<td></td>
<td>Endovascular group</td>
<td>Control group</td>
<td></td>
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<tr>
<td># Enrolled</td>
<td>107</td>
<td>99</td>
<td></td>
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<tr>
<td>1st co-primary outcome (90 D)</td>
<td>UWmRS: 5.5*</td>
<td>UWmRS: 3.4*</td>
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<tr>
<td>2nd co-primary outcome (90 D)</td>
<td>mRS 0-2: 49%*</td>
<td>mRS 0-2: 13%*</td>
<td>3</td>
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<tr>
<td>Primary Safety Outcomes- (90 D mortality)</td>
<td>19%</td>
<td>18%</td>
<td>14%*</td>
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<tr>
<td>Secondary Efficacy</td>
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*Indicates a statistically significant difference*
Acute ischemic strokes = 2667

6-24 hours = 792
NIHSS ≥6 = 1242

6-24 hours and NIHSS ≥6 = 407
ICA/ MCA M1/ M2 Occlusions = 204

DAWN: 45
ET group = 26
% 90d mRS 0-2 = 54%
Non-ET group = 19
% 90d mRS 0-2 = 21%

DEFUSE-3 = 47
ET group = 24
% 90d mRS 0-2 = 38%
Non-ET group = 23
% 90d mRS 0-2 = 17%

Non-DAWN, Non-DEFUSE-3 = 142
ET group = 37
% 90d mRS 0-2 = 30%
Non-ET group = 105
% 90d mRS 0-2 = 12%