DEFUSE 3: 20-year history

- **1990s** - DWI estimates ischemic core; perfusion imaging estimates critically hypoperfused tissue
- **2006** - DEFUSE: MR Target mismatch profile identifies patients who respond favorably to late window thrombolysis
- **2008** - RAPID software: Automated processing of advanced imaging data to estimate the volume of salvageable tissue
- **2012, 2016** - DEFUSE 2 / CRISP: MR/CT Perfusion target mismatch respond favorably to late window thrombectomy
Thank You

- DEFUSE 3 Investigators and coordinators
- 296 patients and family members who signed consent form
- StrokeNet, for unique infrastructure
- NIH, funding all 3 DEFUSE studies
- iSchemaView, for RAPID software platform
- DEFUSE 3 Executive and Endovascular Committees, DSMB, Statisticians, Medical Monitor, Imaging Core Lab, Central IRB
- DEFUSE Research Manager, Stephanie Kemp
Hypothesis and Design

- **Hypothesis:** Stroke patients with MCA and/or ICA occlusion and salvageable tissue identified by CT/MR perfusion benefit from endovascular thrombectomy between 6-16 h.

- **Design:** Eligible patients randomized to thrombectomy (FDA cleared device) vs. medical management alone

- **Endpoint:** Modified Rankin Scale, blinded assessor, day 90
  Primary: ordinal shift analysis; Secondary: mRS 0-2
Key Clinical Inclusion Criteria

- **Age**: 18 - 90 years
- **NIHSS**: $\geq 6$
- **Pre-stroke mRS**: 0 - 2
- **Femoral puncture**: 6 - 16 hours
Key Neuroimaging Inclusion Criteria

1) Occlusion of the ICA and/or MCA M1
   AND

2) RAPID Target Mismatch Profile with core up to 70 ml

Substantially more patients eligible
Early Termination

- A similar late-window study, DAWN, reported positive results in May 2017.
- DEFUSE 3 was placed on hold for an early interim analysis.
- Following this analysis, N = 182, the study was ended.
Patient Accrual

- 182 patients randomized in 1 yr
- Enrollment rate nearly double projected target
- Substantially faster than prior trials
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Endovascular (N = 92)</th>
<th>Medical (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr - median (IQR)</td>
<td>70 (59 - 78.5)</td>
<td>71 (59 - 80)</td>
</tr>
<tr>
<td>NIHSS score - median (IQR)</td>
<td>16 (10 - 20)</td>
<td>16 (12 - 21)</td>
</tr>
<tr>
<td>Stroke onset wake-up (%)</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>Treatment with intravenous tPA (%)</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Qualifying imaging: CT Perfusion</td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>Ischemic core volume, ml - median (IQR)</td>
<td>9 (2 - 26)</td>
<td>10 (2 - 24)</td>
</tr>
<tr>
<td>Perfusion lesion (Tmax&gt;6s) volume, ml - median (IQR)</td>
<td>115 (79-146)</td>
<td>116 (73 - 158)</td>
</tr>
<tr>
<td>Middle cerebral artery occlusion on baseline CTA / MRA</td>
<td>65%</td>
<td>60%</td>
</tr>
</tbody>
</table>
Results: Primary Outcome

Score on Modified Rankin Scale

- 0: 8 patients (8%)
- 1: 4 patients (4%)
- 2: 4 patients (4%)
- 3: 16 patients (16%)
- 4: 27 patients (27%)
- 5: 16 patients (16%)
- 6: 26 patients (26%)

Medical (n = 90)
Results: Primary Outcome

Odds ratio: $2.8 \ (1.6 - 4.7) \quad P<0.0001$

Adjusted odds ratio: $3.4 \ (2.0 - 5.8) \quad P=0.0004$

Number needed to treat: 2
Secondary Outcome (mRS 0–2)

mRS 0–2

45% vs. 17%

P<0.0001
Severe disability/death (mRS 5-6)

mRS 5-6: 22% vs. 42%  \(P=0.0048\)
Reperfusion and Recanalization

<table>
<thead>
<tr>
<th></th>
<th>Endovascular</th>
<th>Medical</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfusion*</td>
<td>79%</td>
<td>18%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recanalization**</td>
<td>78%</td>
<td>18%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* >90% reduction in the Tmax > 6s perfusion lesion at 24 h
** Complete recanalization on MRA/CTA at 24 h
### Primary Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Endovascular</th>
<th>Medical</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic ICH*</td>
<td>6.5%</td>
<td>4.4%</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* 5/6 patients with SICH died in endovascular vs. 2/4 in medical
# Primary Safety Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Endovascular</th>
<th>Medical</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic ICH*</td>
<td>6.5%</td>
<td>4.4%</td>
<td>0.75</td>
</tr>
<tr>
<td>Death</td>
<td>14%</td>
<td>26%</td>
<td>0.05</td>
</tr>
</tbody>
</table>
# DAWN Eligibility

## Treatment effect

<table>
<thead>
<tr>
<th>Status</th>
<th>mRS Shift, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAWN-eligible*</td>
<td>2.7 (1.4 - 5.2)</td>
</tr>
<tr>
<td>DAWN ineligible</td>
<td>3.0 (1.3 - 7.0)</td>
</tr>
</tbody>
</table>

*62% of DEFUSE 3 patients met DAWN eligibility criteria*
<table>
<thead>
<tr>
<th></th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake-up</td>
<td>3.4 (1.6 - 7.4)</td>
</tr>
<tr>
<td>Witnessed onset*</td>
<td>3.4 (1.4 - 8.3)</td>
</tr>
</tbody>
</table>

*Median time to randomization 9.5 hours
Time to Randomization

Treatment effect
mRS shift, OR (95% CI)

Randomized $> 11$ h $\quad 5.7 \ (2.4 \ - \ 13.1)$

Randomized $\leq 11$ h* $\quad 1.7 \ (0.9 \ - \ 3.4)$

*P-value for interaction = 0.07
Functional Outcome (mRS 0-2) at 90 days: Time from Symptom Onset to Randomization

- **Endovascular**
  - < 9 hours: 40%
  - 9-12 hours: 50%
  - > 12 hours: 42%

- **Medical**
  - < 9 hours: 28%
  - 9-12 hours: 17%
  - > 12 hours: 7%
Late Window Paradox

Favorable Outcome (%) Rankin 0-2 at 90 days

<table>
<thead>
<tr>
<th>Group</th>
<th>HERMES Early Window</th>
<th>DAWN + DEFUSE 3 Late Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular</td>
<td>46%</td>
<td>47%</td>
</tr>
<tr>
<td>Control</td>
<td>27%</td>
<td>15%</td>
</tr>
</tbody>
</table>

P = 0.006 for difference in treatment effect
Conclusions

- DEFUSE 3 extends late window therapy to larger population
- Substantial clinical benefit across the disability spectrum
- Two positive trials justify a new standard of care
- Substantial impact on stroke imaging, triage and treatment
- New perspective on “time is brain”

DEFUSE 3 Investigators, NEJM, Jan 24, 2018
DEFUSE 3: Enrollment By Site

40 sites activated; 38 enrolled
0 sites withdrawn