Stanford Stroke Center
DEFUSE 3

Greg Albers, MD
Director, Stanford Stroke Center
Professor of Neurology, Stanford University
DEFUSE 3

Greg Albers, MD
Disclosures: Equity interest and Consultant, RAPID (iSchemaView)
Steering Committee and Core Lab, SWIFT PRIME (Covidien)
THROMBECTOMY DEVICES

First generation

Second generation
(stent retrievers)
RECENT RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

- Stent-retriever + IV tPA vs. IV tPA alone
- Fast endovascular treatment (< 6 hrs)
- Large vessel occlusions (ICA / MCA M1)
- Moderate/Severe deficits (NIHSS 17)
- High rates of reperfusion (TICI 2b/3 of 59-88%)
- NEJM publications (all 5)
New AHA Guidelines 2015

Endovascular therapy with a stent retriever is recommended (Class 1 Level A)

- Proximal MCA or ICA occlusion
- Within 6 hours of symptom onset

We have a New Standard of Care for Stroke!
RECENT RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

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

MR CLEAN
REVASCAT
ESCAPE
SWIFT PRIME
EXTEND-IA
RECENT RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

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

- MR CLEAN
  - P<0.05

- REVASCAT
  - 25%

- ESCAPE
  - 19%

- SWIFT PRIME
  - 33%

- EXTEND-IA

Endovascular

Control

33%

19%
GOOD OUTCOME RATES FOLLOWING ENDOVASCULAR REPERFUSION

MR CLEAN

Fransen P., et al. JAMA Neurol. 2015
Non contrast CT scan
RECENT RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

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

- MR CLEAN
  - CT
  - P<0.05
- REVASCAT
- ESCAPE
- SWIFT PRIME
- EXTEND-IA

Endovascular: 33%
Control: 19%
CT scan: early signs of stroke

ASPECTS SCORE

M2 + 1

ASPECTS = 8
NEW RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

Endovascular

Control

<table>
<thead>
<tr>
<th>Trial</th>
<th>Good Outcome (%)</th>
<th>MR CLEAN P&lt;0.05 CT</th>
<th>REVASCAT P&lt;0.05 ASPECTS</th>
<th>ESCAPE ASPECTS + Collaterals</th>
<th>SWIFT PRIME</th>
<th>EXTEND-IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVASCAT</td>
<td>44%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESCAPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rankin 0-2 at 90 days
ESCAPE Imaging Selection Criteria:
Good scan, proximal occlusion, mod/good collaterals

CTA: ICA T or M1 occl

NCCT ASPECTS 6-10

Single phase CTA: mod/good collaterals or
1st  2nd  3rd phase

Multiphase CTA: mod/good collaterals
RECENT RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Good Outcome (%)</th>
<th>Control</th>
<th>Endovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>P&lt;0.05 CT</td>
<td>19%</td>
<td>33%</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>P&lt;0.05 ASPECTS</td>
<td>28%</td>
<td>44%</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>P&lt;0.001 Collaterals</td>
<td>29%</td>
<td>53%</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTP and MRI Target mismatch</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RAPID MRI Target mismatch

Mismatch map: directly compare volumes of DWI and hypoperfusion

DWI (ADC<620) volume: 10 ml
Perfusion (Tmax>6s) volume: 76 ml

Mismatch volume: 66 ml
Mismatch ratio: 7.6
RAPID CTP Target mismatch

Mismatch map: directly compare volumes of ischemic core & critical hypoperfusion

*tissue with >70% reduction in CBF predicts DWI lesion volume; median absolute error, 9 ml

Cereda et al. JCBFM 2015
STROKE EVOLUTION

Large ischemic core

CBF (%)

Normal

- 25
- 50
- 75

Time (hours)

2 4 24

Reperfusion

Non-contrast CT

CBF

Tmax > 6 s
SWIFT PRIME CASE: SMALL CORE WITH COMPLETE REPERFUSION

Baseline CTP

CBF (< 30%): 11 ml
Perfusion (Tmax>6s) volume: 151 ml

24 h Follow Up CT/CTP

Infarct volume: 12 ml
100% Reperfusion
NO CORE WITH COMPLETE REPERFUSION

Baseline CTP

CBF (0.3 threshold) 0 ml
Hypoperfusion (Tmax>6s) 135 ml

27 h Follow Up MRI

Infarct Volume 1 ml
100% Reperfusion
RECENT RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

**Good Outcome (%) Rankin 0-2 at 90 days**

- **MR CLEAN P<0.05 CT**
  - Endovascular: 33%
  - Control: 19%

- **REVASCAT P<0.05 ASPECTS**
  - Endovascular: 44%
  - Control: 28%

- **ESCAPE P<0.001 Collaterals**
  - Endovascular: 53%
  - Control: 29%

- **SWIFT PRIME P<0.001 CTP/MRI (90%)**
  - Endovascular: 60%
  - Control: 36%

- **EXTEND-IA CTP (100%)**
  - Endovascular: 60%
  - Control: 36%
EXTEND-IA: Ischemic Core >70 ml

- Ischemic Core: 73 ml
- Perfusion (Tmax>6s) lesion: 88 ml
- Mismatch ratio: 1.2
- Absolute Mismatch Difference: 16 ml
- Mismatch > 1.2: YES
- Absolute mismatch > 10 ml: YES
- Ischemic Core < 70 ml: NO
- Randomize patient: NO
RECENT RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Endovascular (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN P&lt;0.05 CT</td>
<td>33%</td>
<td>19%</td>
</tr>
<tr>
<td>REVASCAT P&lt;0.05 ASPECTS</td>
<td>44%</td>
<td>28%</td>
</tr>
<tr>
<td>ESCAPE P&lt;0.001 Collaterals</td>
<td>53%</td>
<td>29%</td>
</tr>
<tr>
<td>SWIFT PRIME P&lt;0.001 CTP/MRI 90%</td>
<td>60%</td>
<td>36%</td>
</tr>
<tr>
<td>EXTEND-IA P&lt;0.01 CTP 100%</td>
<td>71%</td>
<td>40%</td>
</tr>
</tbody>
</table>
EXTENDING THE WINDOW FOR REPERFUSION THERAPY WITH ADVANCED IMAGING:

- **Endovascular therapy**
  - DEFUSE 3 (6-16 hours)
  - DAWN (6-24 hours)
  - POSITIVE (6-12 hours)
  CTP or MR (Target mismatch)
  CTP or MR (small core)
  CTP or MR (local criteria)

- **Intravenous thrombolysis**
  - EXTEND (4.5-9 hours)
  - ECASS 4 (4.5-9 hours)
  CTP or MR (Target mismatch)
  MRI (local mismatch criteria)
GOOD OUTCOME RATES FOLLOWING ENDOVASCULAR REPERFUSION

MR CLEAN

DEFUSE 2
MRI Target Mismatch

Fransen P., et al. JAMA Neurol. 2015
CRISP: CT PERFUSION STUDY

ALL REPERFUSED PATIENTS (N=164)

Lansberg, et al. ISC 2016

Tsai, et al. ISC 2016

p=0.08
CRISP:

REPERFUSED CTP TARGET MISMATCH (N=111)

p=0.47

Tsai, et al. ISC 2016
Initial Growth Rate: Known Onset & M1 Occlusion

Initial Growth Rate: Known Onset & M1 Occlusion

DEFUSE 3 Sites
DEFUSE 3: Study Design

- Prospective, Randomized, Open-treatment, Blinded Endpoint, Adaptive trial
- 476 patients at 45 sites
- 1:1 randomization: endovascular vs. medical therapy

6-16 hours after stroke onset
Clinical Inclusion Criteria

- Signs and symptoms consistent with an acute anterior circulation stroke
- Age 18-90 years
- Baseline NIHSSS ≥ 6 immediately prior to randomization
- Endovascular treatment (femoral puncture) between 6-16 hours of stroke onset (onset is defined as time last known well)
- Pre-stroke mRS score 0-2 (= functionally fully independent for all ADLs)
- Patient or Legally Authorized Representative has signed Informed Consent
Clinical Exclusion Criteria

- Other serious, advanced, or terminal illness or life expectancy <6 months
- Pre-existing neurological /psychiatric disease that would confound evaluations
- Pregnancy
- Unable to undergo a contrast brain perfusion scan with either MRI or CT
- Known allergy to iodine that precludes an endovascular procedure
- Treated with tPA >4.5 hrs after last known well (ECASS III criteria apply if 3-4.5)
- Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; oral anticoagulant with INR > 3 (recent use of new oral anticoagulants ok if eGFR > 30 ml/min)
DEFUSE 3: Neuroimaging Criteria

1) MRA / CTA demonstrates
   • M1 segment MCA occlusion, or
   • ICA occlusion (cervical or intracranial; with or without tandem MCA lesions)

AND

2) Target Mismatch Profile on CT perfusion or MRI (RAPID)
   • Ischemic core < 70 mL
   • Mismatch ratio ≥ 1.8
   • Mismatch ≥ 15 mL
M2 Superior

M2 Inferior
Axial MIP from CTA- Left MCA M1 Occlusion in the horizontal segment of the MCA, prior to the genu. Qualifies for randomization.
Axial MIP from CTA- Left MCA M2 Occlusion just distal to the genu

Does not qualify for randomization
CBF (<30%) volume: 16.6 ml
Perfusion (Tmax>6.0s) volume: 142.6 ml
Mismatch volume: 126.0 ml
Mismatch ratio: 8.6
May 6, 2016; Stanford site
64 yo with L sided paralysis
7.5 hours after onset

DWI (ADC<630) volume: 5.9 ml
Perfusion (Tmax >6s) volume: 108.6 ml
Mismatch volume: 102.7 ml
Mismatch ratio: 18.4 ml
May 6, 2016; Stanford site
64 yo with L sided paralysis
7.5 hours after onset
Conclusions

• Endovascular therapy within 6 hrs of onset for patients with MCA M1 or ICA occlusions is highly effective and safe using modern stent-retrievers

• Optimal patient selection and prompt triage to endovascular centers is essential

• Patients with small ischemic core lesions who achieve complete reperfusion have exceptional clinical outcomes

• Infarct growth rates are highly variable (tissue vs. time)

• Future studies will clarify the role of endovascular therapy in extended time windows
Stanford Stroke Center

Vascular Neurology

Greg Albers, MD
Stephanie Casal, RN, MS, CNS
Paul George, MD PhD
Anna Finley, MD
Karen Hirsh, MD
Maarten Lansberg, MD, PhD
Neil Schwartz, MD, PhD
Isa San Pedro, RN
Chitra Venkat, MD
Nirali Vora, MD

Interventional Neuro IR

Michael Marks, MD
Mary Brethour, PhD, APN
Huy Do, MD
Rob Dodd, MD, PhD
Jeremy Heit, MD, PhD
Mary Marcellus, RN

Viet Nguyen, MD

Cerebrovascular Surgery

Gary Steinberg, MD, PhD
Teresa Bell -Stephens, RN
Steve Chang, MD
Rob Dodd, MD, PhD
Joli Vavao, RN, NP

NeuroCritical Care

Karen Hirsh, MD
Marion Buckwalter, MD, PhD
Anna Finley, MD
Kyle Hobbs, MD
Chitra Venkat, MD

Stroke Rehabilitation

Kara Flavin, MD

Intraoperative Monitoring

Jaime Lopez, MD
Charlie Cho, MD
Leslie Lee, MD

Max Wintermark, MD, PhD
Roland Bammer, PhD
Soren Christensen, PhD
Nancy Fischbein, MD
Mike Moseley, PhD
Michael Mlynash, MD
Greg Zaharchuk, MD