OPTIMAL PATIENT SELECTION FOR ENDOVASCULAR THERAPY: ROLE OF PENUMBRAL IMAGING

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Disclosures: Equity interest and Consultant, RAPID (iSchemaView)
Steering Committee and Core Lab, SWIFT PRIME (Covidien)

Randomized Endovascular Trials
NEJM 2013

- Synthesis
- IMS III
- MR Rescue
What Went Wrong?

THROMBECTOMY DEVICES

First generation

Second generation
(stent retrievers)

NEW 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)

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

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

- MR CLEAN
- REVASCAT
- ESCAPE
- SWIFT PRIME
- EXTEND-IA

Endo-vascular: 33%
Control: 19%

Aspects Score

CT scan: early signs of stroke
ASPECTS SCORE

ASPECTS = 9
NEW RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Endovascular</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN + CT</td>
<td>33%</td>
<td>19%</td>
</tr>
<tr>
<td>REVASCAT + ASPECTS</td>
<td>44%</td>
<td>28%</td>
</tr>
<tr>
<td>ESCAPE + Collaterals</td>
<td>53%</td>
<td>29%</td>
</tr>
</tbody>
</table>

ESCAPE Imaging Selection Criteria:
Good scan, proximal occlusion, mod/good collaterals

CT: ICA T or M1 ocl
NCT ASP.CTS 6-10
Multiple CTA: mod/good collaterals

NEW RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY
RAPID outputs MRI
Mismatch map: directly compare volumes of DWI and hypoperfusion

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

RAPID outputs
Location of RAPID selected arterial input/venous output and graph

* AIF / VOF output is the same for both CTP and MRI
Why was RAPID developed?

- To extend the treatment window for patients with salvageable tissue
- To avoid administering futile or harmful reperfusion therapies

68 YO, APHASIA, R HEMIPARISIS
4 HRS FROM ONSET, NORMAL CT
ENDOVASCULAR CANDIDATE?

STROKE EVOLUTION
Large ischemic core
MALIGNANT PROFILE

Large ischemic core

Baseline CTP

CBF (>3 thresholds) 182 ml
Hypoperfusion (Tmax>6s) 215 ml

Non-contrast CT at baseline

MRI at 48 h

SWIFT PRIME: RAPID OUTPUT MAP

Estimated core 9 ml

Hypoperfusion (Tmax>6s) 172 ml

Mismatch volume: 158 ml
Mismatch ratio: 19.3

Estimated core: < 50% YES
Mismatch volume: > 150 and < 300 YES
(Tmax > 6s) => > 150% YES

SWIFT PRIME CASE: SMALL CORE WITH COMPLETE REPERFUSION

Baseline CTP

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

24 h Follow up CTP

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

Baseline CTP
CBF (S.3 threshold): 6 ml
Hypoperfusion (Tmax>6s): 136 ml

27 h Follow Up MIPH
Infarct Volume: 1 ml
100% Reperfusion

NEW RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

<table>
<thead>
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<th>Trial</th>
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<td>ASPECTS</td>
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</tr>
<tr>
<td>ESCAPE</td>
<td>60%</td>
<td></td>
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<tr>
<td>SWIFT PRIME: RAPID</td>
<td></td>
<td></td>
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<tr>
<td>EXTEND-IA</td>
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Endovascular Control 19% 28% 29% 36%

EXTEND-IA: Target mismatch

Infarct Core: 24 ml Perfusion (Tmax>6s) lesion: 119 ml
Mismatch ratio: 5.0 Absolute Mismatch Difference: 95 ml
Mismatch > 1.5: YES
Absolute mismatch > 10 ml: YES
Infarct Core < 70 ml: YES
Randomize patient: YES

P<0.05
P<0.05
P<0.05
P<0.001
P<0.001
P<0.001
EXTEND-IA: Ischemic Core >70 ml

NEW RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY

<table>
<thead>
<tr>
<th>Trial</th>
<th>0%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
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</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
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<tr>
<td>SWIFT PRIME</td>
<td></td>
<td></td>
<td></td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71%</td>
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Endovascular: 33% 44% 53% 60% 71%
Control: 19% 28% 29% 36% 40%

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!
DEFUSE and DEFUSE 2

- Patients with Target mismatch profile have a powerful association between reperfusion and favorable clinical outcomes following intravenous tPA:
  - Magnetic Resonance Imaging Profiles Predict Clinical Response to Early Reperfusion: The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study
    - Annals of Neurology, 2006

- And following endovascular therapy:
  - MRI Profile and Response to Endovascular Reperfusion After Stroke (DEFUSE 2): A Prospective Cohort study
    - Lancet Neurology, 2013

Target mismatch profile

<table>
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<tr>
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<th>Baseline</th>
<th>24 hours</th>
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<tbody>
<tr>
<td></td>
<td>ischemic core</td>
<td>hypo-perfusion</td>
</tr>
<tr>
<td>TMM with successful reperfusion</td>
<td><img src="image1" alt="Image of TMM with successful reperfusion" /></td>
<td></td>
</tr>
<tr>
<td>TMM without successful reperfusion</td>
<td><img src="image2" alt="Image of TMM without successful reperfusion" /></td>
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RAPID Software (Stanford / iSchemaViewRAPID)

SWIFT PRIME: Infarct Prediction using RAPID

RAPID ischemic core and hypoperfusion volumes predicted infarct size

- Baseline core predicts infarct volume in reperfusers
- Baseline hypoperfusion predicts infarct in non-reperfusers
- Malignant profile predicts infarct growth despite reperfusion


TMM Patients in SWIFT PRIME (80% CT Perfusion, 20% MRI)

- Core predicts infarct volume in pts with >90% reperfusion
- Union core + f/u Tmax>6s predicts infarct volume

TMM Patients in DEFUSE 2 (all MRI)

- DWI predicts infarct volume in pts with >90% reperfusion
- Union DWI + f/u Tmax>6s predicts infarct volume
SWIFT PRIME: Infarct volume strongly correlates with clinical outcome

DEFUSE 2: Infarct growth and reperfusion

SWIFT PRIME: Degree of reperfusion strongly correlates with clinical outcome

Albers GW, et al. Stroke, August 2015

Federau, et al. Radiology, in press
DEFUSE 2: Response to reperfusion is not time-dependent in patients with salvageable tissue


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DEFUSE 3: Premise

Infarct growth is highly variable

Many patients have salvageable tissue beyond 6 hours

Advanced CT/MR imaging can identify these patients

These patients will benefit from modern endovascular therapies
DEFUSE 3: NIH-funded, prospective, randomized, multi-center, adaptive, blinded endpoint trial

- Paradigm shift
  - From time-based selection to imaging-based selection

- Target population
  - Anterior circulation ischemic stroke; ICA or M1 occlusions (CTA/MRA)
  - Salvageable tissue on CT perfusion or MR diffusion / perfusion
  - Endovascular therapy within 6-16 hours of last known well

- Design
  - 1:1 randomization; standard medical therapy vs. endovascular
  - 45 sites

Neuroimaging Inclusion Criteria

MRA / CTA reveals
- M1 segment MCA occlusion, or
- ICA occlusion (cervical or intracranial; with or without tandem MCA lesions)

AND

Target Mismatch Profile on
CT perfusion or MRI (RAPID)
- Ischemic core volume < 70 mL
- Mismatch ratio > 1.8
- Mismatch volume ≥ 15 mL

RAPID in DEFUSE 3

FDA cleared research version of RAPID, (courtesy of iSchemaView) installed at each site to ensure uniformity in:

- Image acquisition
- Processing time
- Image quality
- Physician interpretation
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
New Randomized Clinical Trials of Endovascular Therapy: Imaging Selection

<table>
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<th>Trial</th>
<th>TICI 2b/3 Rates</th>
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<tr>
<td>MR CLEAN</td>
<td>59%</td>
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<tr>
<td>REVASCAT</td>
<td>66%</td>
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<tr>
<td>ESCAPE</td>
<td>72%</td>
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<tr>
<td>SWIFT PRIME</td>
<td>88%</td>
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<td>EXTEND-IA</td>
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Control 19% 28% 29% 36% 40%

New Randomized Clinical Trials of Endovascular Therapy: Rankin 0-2 at 90 days

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Control 19% 28% 29% 36% 40%

New Randomized Clinical Trials of Endovascular Therapy: Onset to femoral puncture

<table>
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<th>Onset to 1st reperfusion</th>
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<tbody>
<tr>
<td>MR CLEAN</td>
<td>269 min</td>
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<tr>
<td>REVASCAT</td>
<td>269 min</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>241 min</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>224 min</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>210 min</td>
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Control 19% 28% 29% 36% 40%

*Onset to 1st reperfusion