ENDOVASCULAR ACUTE STROKE THERAPY: INTEGRATING IMAGING INTO TREATMENT DECISIONS

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DISCLOSURES

Consultant/Advisory Board: Ownership Interest: Silk Road Medical – modest
Consultant/Advisory Board: Covidien/Medtronic: unpaid
Consultant: Stryker Neurovascular unpaid
PI: REVASCAT (Fundacio Ictus Malaltia Vascular), unpaid
PI: DAWN (Stryker Neurovascular), unpaid
ROLE OF IMAGING IN SELECTION FOR ACUTE STROKE REPERFUSION THERAPIES IN THE HYPERACUTE TIME WINDOW (0-6 hours)

- Rule out hemorrhage
- Rule out absence of occlusion
- Rule out large core
- Rule out absence or small of “at risk” tissue

MAIN ROLE OF IMAGING IS TO EXCLUDE PATIENTS FROM TREATMENT !!!
Ischemic Penumbra
Initial Growth Rate: Known Onset & M1 Occlusion

Baseline DWI Volume (ml)

Time between Symptom Onset and Baseline MRI (hrs)

DEFUSE 2

Initial Growth Rate: Known Onset & M1 Occlusion

Baseline DWI Volume (ml)

Time between Symptom Onset and Baseline MRI (hrs)

## SELECTION FOR REPERFUSION IN PATIENTS WITH LARGE VESSEL OCCLUSION

<table>
<thead>
<tr>
<th>Likely to Benefit</th>
<th>Unlikely to Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small core</td>
<td>Any size core (usually large)</td>
</tr>
<tr>
<td>Large penumbra</td>
<td>Small penumbra</td>
</tr>
<tr>
<td><strong>MISMATCH</strong></td>
<td><strong>NO MISMATCH</strong></td>
</tr>
</tbody>
</table>
IMS 3  24 hour infarct volume by 90 days mRS categories

* Median 24 hr volume
P < 0.0001 by ANOVA

Jovin et al., ISC 2015
PRE-TREATMENT ISCHEMIC CORE A POWERFUL DETERMINANT OF OUTCOME IN ACUTE STROKE

- CT based (ASPECTS), Hill et al., Stroke 2003
- CTP based (CBV), Lev at al., Stroke 2001
- Xenon-CT-CBF based (core voxels), Jovin et al, Stroke 2003
- MRI based (DWI), Yoo et al., Stroke 2009 (DWI cutoff of 70 cc’s predicts poor outcome)
- MRI based (DWI), Parsons et. al, Journal Cereb Blood Metab 2010 (DWI cut off 25 cc)
Figure 1: ASPECTS study form

- Anterior circulation: Prolateral circulation: C:caudate; L: lentiform; Ic: Internal capsule; Insular ribbon; MCA: Middle cerebral artery
- M1: Anterior MCA cortex
- M2: MCA cortex lateral to Insular ribbon
- M3: Posterior MCA cortex
- M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia.

Subcortical structures are allotted 3 points (C, L, and IC); MCA cortex is allotted 7 points (Insular cortex, M1, M2, M3, M4, M5, and M6).
The clinical–DWI mismatch
A new diagnostic approach to the brain tissue at risk of infarction

A. Dávalos, MD, PhD; M. Blanco, MD, PhD; S. Pedraza, MD; R. Leira, MD, PhD; M. Castellanos, MD; J.M. Pumar, MD, PhD; Y. Silva, MD; J. Serena, MD, PhD; and J. Castillo, MD, PhD

Abstract—Objective: To evaluate the usefulness of a mismatch between the severity of acute clinical manifestations and the diffusion-weighted imaging (DWI) lesion in predicting early stroke outcome and infarct volume. Methods: One hundred sixty-six patients with a hemispheric ischemic stroke of <12 hours’ duration were studied. The NIH Stroke Scale (NIHSS) score and the volume of DWI lesion were measured on admission and at 72 ± 12 hours. Infarct volume was measured on T2-weighted or fluid-attenuated inversion recovery images at day 30. Early neurologic deterioration (END) was defined as an increase of ≥4 points between the two NIHSS evaluations. Thirty-eight patients received IV thrombolysis or abciximab. Clinical–DWI mismatch (CDM) was defined as NIHSS score of ≥8 and ischemic volume on DWI of ≤25 mL on admission. The adjusted influence of CDM on END, DWI lesion enlargement at 72 hours, and infarct growth at day 30 was evaluated by logistic regression analysis and generalized linear models. Results: CDM was found in 87 patients (52.4%). Patients with CDM had a higher risk of END than patients without CDM because NIHSS < 8 (odds ratio [OR], 9.0; 95% CI, 1.9 to 42) or DWI lesion > 25 mL (OR, 2.0; 95% CI, 0.8 to 4.9). CDM was associated with an increase of 46 to 68 mL in the mean volume of DWI lesion enlargement and infarct growth in comparison with non-CDM. All the effects were even greater and significant in patients not treated with reperfusion therapies. Conclusions: Acute stroke patients with an NIHSS score of ≥8 and DWI volume of ≤25 mL have a higher probability of infarct growth and early neurologic deterioration. The new concept of CDM may identify patients with tissue at risk of infarction for thrombolytic or neuroprotective drugs.

NEUROLOGY 2004;62:2187–2192
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

CT VS CTP AS SELECTION TOOL FOR ENDOVASCULAR THERAPY- A MULTICENTER STUDY

N=338 patients from 7 US centers
Mean age 67, mean NIHSS 18
Occlusion location: 248 (73%) M1, 55 (17%) ICA terminus, 35 (10%) M2
sICH rates: CTP vs CT 6.8% vs. 6.6%, p=0.82
Good outcomes: CTP vs. CT 36.5% vs. 38.9%, p=0.72
Final infarct volume: 80±64 cm³ vs. 88±62 cm³, p=0.32
CT acquisition to groin puncture times: 132±57 mins. vs. 97±60 mins., p=0.01
CT acquisition to reperfusion times: 227±109 mins. vs. 199±91 mins., p<0.001

Gupta et al., JNIS 2012
Median TIMES across recent trials (min median)

<table>
<thead>
<tr>
<th></th>
<th>ESCAPE</th>
<th>SWIFT PRIME</th>
<th>REVASCAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging to puncture</td>
<td>50</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>Imaging to perfusion</td>
<td>82</td>
<td>100</td>
<td>138</td>
</tr>
<tr>
<td>Onset to puncture (MR CLEAN 260)</td>
<td>180</td>
<td>224</td>
<td>270</td>
</tr>
<tr>
<td>Onset to perfusion (IMS 325)</td>
<td>213</td>
<td>268</td>
<td>356</td>
</tr>
<tr>
<td>Door to groin</td>
<td>89</td>
<td>95</td>
<td>109</td>
</tr>
</tbody>
</table>
WHAT IS THE PRICE WE PAY FOR THE ADDITIONAL TIME REQUIRED FOR IMAGING ???

FIGURE 3: Predicted probability and confidence interval of good neurological outcome (mRS 0–2) at 90 days from logistic regression with time as a continuous variable. Probability of mRS 0 to 2 is plotted against onset to recanalization. Dashed lines demonstrate 95% confidence intervals. mRS = modified Rankin Scale.

FIGURE 4: Predicted 90-day mRS outcomes from adjusted ordinal logistic regression. Stacked bar graphs represent the predicted mRS outcome distributions for each incremental 60-minute change in onset-to-reperfusion time, beginning with 180 minutes. Numbers within each colored region represent the percentage of patients with the corresponding mRS outcome grade for that time window. mRS = modified Rankin Scale. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

| TABLE 4. Benefit Associated With Every 15-Minute Acceleration of Substantial Reperfusion |
|---------------------------------|-----------------|-----------------|
|                                 | Number Needed to Treat | Benefit Per Thousand Treated |
| For transitions across multiple mRS levels |                        |                              |
| All seven levels (0, 1, 2, 3, 4, 5, 6) | 30                | 34                           |
| Best six levels (0, 1, 2, 3, 4, 5/6)   | 30                | 34                           |
| For individual dichotomizations of the mRS |                        |                              |
| 0 vs. 1–6                          | 104               | 10                           |
| 0–1 vs. 2–6                        | 48                | 21                           |
| 0–2 vs. 3–6                        | 46                | 22                           |
| 0–3 vs. 4–6                        | 58                | 17                           |
| 0–4 vs. 5–6                        | 115               | 9                            |
| 0–5 vs. 6                          | 140               | 7                            |

mRS = modified Rankin Scale.
## REVASCAT: Outcomes by CTP/MRI vs No CTP/MRI

### 1 mRS by CTP or MRI

<table>
<thead>
<tr>
<th></th>
<th>CTP or MRI</th>
<th>Not CTP and MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>mRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no-missing</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>0-2</td>
<td>14 (45.2%)</td>
<td>10 (30.3%)</td>
</tr>
<tr>
<td>3-6</td>
<td>17 (54.8%)</td>
<td>23 (69.7%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Logistic Regression mRS 0-2 (OR 95%) / CMH

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI) for mRS 0-2</th>
<th>OR IC 95% for mRS 0-2 CMH</th>
<th>OR (95% CI) shift analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (Exp vs Med)</td>
<td>1.985 (1.111 – 3.546)</td>
<td>1.985 (1.112 -3.546)</td>
<td>1.685 (1.032 – 2.751)</td>
</tr>
<tr>
<td>CTP or MRI (No vs Yes)</td>
<td>0.889 (0.487 – 1.654)</td>
<td>1.158 (0.684 - 1.963)</td>
<td></td>
</tr>
</tbody>
</table>
IMAGING BASED EXCLUSION AND TREATMENT EFFECT

Absolute difference between groups in mRS 0-2

Median time from onset to groin puncture, min

EXTEND IA$^2$ NNT=3
ESCAPE$^1$ NNT=4
SWIFT PRIME$^3$ NNT=4
MR CLEAN$^4$ NNT=8
REVASCAT$^5$ NNT=6

Perfusion imaging/mismatch
ASPECT score $\geq$ 6
No CT/MRI criteria

† Moderate-good collaterals
‡ Performed in 81% of patients

$^1$Goyal et al., NEJM 2015, $^2$Campbell et al., NEJM 2015, $^3$Saver et al., NEJM 2015, $^4$Berkhemmer et al., NEJM 2015, $^5$Jovin et al., NEJM 2015
23 Randomized Trials of PCI vs Lytics: 30 day Events (n=7739)

ARR 6%, NNT= 29

Keeley & Grines, Lancet 2003;361:13-20
Clinical Vignette #2

59 year old man who presented with NSTEMI and heart failure in the setting of RCA occlusion requiring CABG and valve repair.

After extubation: NIHSS 16 (1 LOCC, 2 VF, 2 gaze, 4 LLE, 4 LUE, 1 sensation, 2 neglect).

What next?

Tpa?
Additional imaging?
Thrombectomy?
Clinical Vignette

CT head obtained on angio table: No hemorrhage
DSA reveals right M1 occlusion and favorable collaterals.
Clinical Vignette

Last seen well
Symptoms
Angio suite
CT head
Access
Recanalization

9.5 hours → 50 minutes → 20 minutes → 5 minutes → 30 minutes

Dual energy CT

Process
Symptom-CT: 70 minutes
Picture-Puncture: 5 minutes
Puncture-Treatment: 30 minutes
Direct transfer to angiosuite

- Jan 2013 to July 2015: review of 379 patients undergoing endovascular therapy at UPMC

- 8.9% were triage directly from helipad to the angio-suite

- Mean door to puncture time: 21.1 minutes

Kenmuir et al (submitted)
Example workflow of left MCA occlusion
Comparison with “gold standard”: CT-Perfusion

CT at presentation

Artis at presentation

DynaCT-Angio

DynaPBV Neuro

(Image courtesy of Prof. Dörfler and Dr. Struffert, Neuroradiology, Erlangen)
### Overview

<table>
<thead>
<tr>
<th>Title</th>
<th>DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Stryker Neyrovascular Inc.</td>
</tr>
<tr>
<td>PIs</td>
<td>Tudor G. Jovin, MD and Raul G. Nogueira, MD</td>
</tr>
<tr>
<td>Funding</td>
<td>Stryker Neurovascular Inc.</td>
</tr>
<tr>
<td>Study device</td>
<td>Trevo® ProVue™ and Trevo® XP ProVue™ Retrievers</td>
</tr>
<tr>
<td>Control intervention (IV-tPA yes/no?)</td>
<td>Best medical therapy including iv t-PA in eligible patients (which will be estimated to make up maximum 20% of total)</td>
</tr>
<tr>
<td>Study population</td>
<td>Acute stroke patients with no upper age limit presenting in the 6-24 hour time window with proximal anterior circulation occlusions (M1, ICA T) and substantial clinical/core mismatch</td>
</tr>
<tr>
<td>Objective</td>
<td>To evaluate the hypothesis that Trevo thrombectomy plus medical management leads to superior clinical outcomes at 90 days as compared to medical management alone in appropriately selected subjects experiencing an acute ischemic stroke when treatment is initiated within 6-24 hours after last seen well.</td>
</tr>
</tbody>
</table>
Conclusions

• In the hyperacute time window we are still excluding patients from treatment who may benefit even when selection is based on plain CT (ASPECTS)
• Advanced imaging only excludes more patients without a clear safety advantage
• Advanced imaging is associated with delays that translate into fewer favorable outcomes
• Characterization of core thresholds beyond which there is no benefit or harm is a priority for the field
• In the meantime focus should be on time with imaging only used to exclude large core (ASPECTS < 5 or > 1/3 MCA hypodensity)
• In the > 6 hour time window target population consists of “slow progresors”. Time to reperfusion less impactful and info derived from imaging may be worth it
UPMC ACUTE ENDOVASCULAR STROKE TEAM