What Have We Learned: Selection for Endovascular Stroke Therapy

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Disclosures:

Stryker Neurovascular/ Concentric Medical
- Trevo-2 Trial PI, DAWN Trial PI
- Physician Advisory Committee

Covidien/ ev3 Neurovascular
- SWIFT and SWIFT-PRIME Trial Steering Committee
- STAR Trial Core Lab, Physician Advisory Committee, Onyx Proctor

Penumbra
- 3-D Separator Trial Executive Committee

Coaxia
- Physician Advisory Committee

Rapid Medical
- Physician Advisory Committee, Consultant
Acute Reperfusion Therapy
Patient Selection
Patient Selection:

- Proximal Arterial Occlusion
- Significant Clinical Deficit
- Limited Infarct Core
- Age vs. Functional Status
- Time to Treatment?
  - Safety data (PROACT-II, MERCI, Multi MERCI, Penumbra trials) for < 8 hours from onset
  - Advanced Imaging (MRI or CTP) for > 8 hours, unknown time of onset, and wake-up strokes currently under investigation in the DAWN Trial
  - Vertebrobasilar occlusion with severe deficits: just do it!
Imaging Selection and Core
Mismatch vs. Penumbra: Basic Concepts

- Mismatch
  - vessel occlusion
  - hypoperfused tissue
  - tissue at risk

- Infarct core

Mismatch vs. Penumbra: Basic Concepts
Mismatch vs. Penumbra: A Word of Caution

✓ Penumbra equals not only regions of DWI-PWI mismatch but also a portion of the DWI abnormality itself.

✓ PWI includes areas of benign oligemia.

Infarct Core Estimation:

- **Non-Contrast CT ASPECTS**
  - Fast
  - Less Reliable
  - Higher Inter-Rater Variability
  - Poor correlation with Infarct Volumes

- **CTA-SI ASPECTS**
  - Easier but may overestimate core
    

- **CTA Collaterals**
  

- **CTA Collaterals CALGARY**

- **CT Perfusion Core**
  - rCBF<30% (RAPID)

- **DWI Core**
  - Gold Standard second only to PET
Imaging Selection Menu:

Penumbra Estimation

- **Perfusion Imaging**
  - $T_{\text{max}} > 4 \text{ sec} = \text{Benign Oligemia}$
  - $T_{\text{max}} > 6 \text{ sec} = \text{Penumbra}$
  - $T_{\text{max}} > 10 \text{ sec} = \text{Critical Penumbra/Imminent Core}$

- **Clinical Core Mismatch**
  - $b\text{NIHSS} \geq 8$ and $\text{DWI volume} \leq 25\text{cc}$
    
  - **DAWN**
    a. 0-20 cc core infarct and NIHSS $\geq 10$ (and age $\geq 80$ years old)
    b. 0-30 cc core infarct and NIHSS $\geq 10$ (and age $< 80$ years old)
    c. 31 cc to $< 50$ cc core infarct and NIHSS $\geq 20$ (and age $< 80$ years old)
Why I Use CT?

Advantages
- Available
- Fast
- Quantitative
- Low cost
- Accurate CTA

Disadvantages
- Contrast limits over 1st 24-hrs
  - Radiation risk minimal
- Variable coverage
- DWI more sensitive for core
  - Lacunes, small emboli

But CT Perfusion is Good Enough!

Straka M. ISC 2012
RAPID Processing

Auto Image Analysis:
• motion & time correction
• AIF & VOF selection
• deconvolution & map generation
• CTP or DWI and PWI lesion segmentation
• Lesion volume calculation
83 yo Man – NIHSS 14 – CTA Right M2 Cutoff – Not IV TPA Candidate – Patient/Family Declined IAT

RAPID: Prediction of Core and Penumbra

CBF–based Core

Tmax

Estimated core 2 ml

Hypoperfusion (Tmax>6s) 57 ml

Mismatch volume: 55 ml
Mismatch ratio: 28.6

NOTE: Add volumes from BOTH slabs to determine eligibility:
Joint estimated core <= 50ml?
Joint mismatch volume > 15ml and ratio > 1.8?
Joint (Tmax>10s) <=100ml?
RAPID: Lack of Reperfusion and Core Progression in to Predicted Penumbra
How Much is Too Much (Infarct Core)?

It depends on our goals:

- **Functional Independence (90-day mRS 0-2):**
  - ASPECTS > 7 (Hill et al., Stroke 2003)
  - Volume < 30-40 mL (less if age > 80) (Zaidi S, Nogueira RG, Jovin TG et al. Stroke. 2013)
  - Little chance if Volume > 70 mL (Yoo AJ et al. Stroke 2009)

- mRS Shift – every mL brain volume likely matters…
  - ASPECTS 5-7 likely reasonable
  - Volumes 50-100 mL likely reasonable

- **Prevent hemicraniectomy or death**
  - Can we carefully consider Volumes > 100 mL/ > 1/3 MCA Territory?
  - The risks is SICH/Edema > 100 ML (Albers GW et al, Ann Neurol 2006)
Endovascular Therapy in ASPECTS 5-7

- LVOS with ASPECTS 5-7 treated with IAT (n=86) or medical therapy alone (± IV t-PA; n=15) at two centers from 2009-2012
- Age (67±14 vs. 67±19yrs) and bNIHSS (20±5 vs. 20±6) similar in IAT vs. Medical.
- IAT: mTICI≥2B=67%; ICH: Symptomatic=10%; Asymptomatic=36%
- IAT 90-day Outcomes: mRS≤2=20%; mRS≤3=33%; Death=43%
- Successful IAT reperfusion = smaller FIV (p=0.015) and higher rates of good (p=0.02) and acceptable (p=0.03) outcomes.
- Strong trend towards a higher hemicraniectomy requirement in medical vs. endovascular pts (20% vs. 6%, p=0.06) despite similar in-hospital mortality.
- Median FIV significant lower with IAT vs. medical therapy (80ml[IQR, 38-122] vs. 190ml[121-267], p=0.015).
3 out of 40 BAO pts who had extensive bilateral pontine DWI changes and achieved 90-day mRS 0-2

Patient #1: 18 year-old man with embolic BAO due to a PFO. 90-day mRS=0

Patients #2 (age 73) and #3 (age 56) had atherosclerotic occlusions that required adjunctive intracranial stenting and angioplasty, respectively. 90-day mRS 1 and 2, respectively
Thrombectomy and Age
Thrombectomy in the Elderly:

91y/o female; NIHSS: 23 ; S/p Full IV dose rt-PA
- Post Merci L6 x 2 + 75k u of UK
- TICI 3 Recanalization
- 90-day mRS:0
### OCTOGENERIANS POOLED ANALYSIS
**MERCI/MULTIMERCI/REGISTRY N=233**

Nogueira RG, ISC 2010

<table>
<thead>
<tr>
<th>90d Outcomes</th>
<th>All Pts (n= 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0-2</td>
<td>17.3% (40/231)</td>
</tr>
<tr>
<td>mRS 6</td>
<td>55.2% (128/232)</td>
</tr>
</tbody>
</table>

However, age is an imperfect surrogate of functional status

Age = Population

Functional Status = Your Patient!
IAT in the Elderly Revisited:

- Single Center 102 Consecutive IAT for pts ≥80 yrs - Sept.2010-Sept.2014
  - Age: 84.8 yrs (80-100)
  - bNIHSS: 19.2 (4-33)
  - ASPECTS ≥7: 58%

**TABLE 2: Clinical and Radiographic outcome**

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Overall (n=97)</th>
<th>Stentretreiver (n=54)</th>
<th>ASPECTS ≥7 (n=56)</th>
<th>CT Perfusion (n=31)</th>
<th>IV t-Pa (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-Day Good outcome (mRS 0-2)</td>
<td>26/97(27%)</td>
<td>18/54(33%)</td>
<td>16/56(29%)</td>
<td>11/31(35%)</td>
<td>14/50(28%)</td>
</tr>
<tr>
<td>Symptomatic Hemorrhage</td>
<td>8/97(8%)</td>
<td>5/54(9%)</td>
<td>3/56(5%)</td>
<td>1/31(3%)</td>
<td>4/50(8%)</td>
</tr>
<tr>
<td>90-Day Mortality</td>
<td>42/97(43%)</td>
<td>20/54(37%)</td>
<td>22/56(39%)</td>
<td>13/31(42%)</td>
<td>20/50(40%)</td>
</tr>
</tbody>
</table>

- Control pts ≥80 yrs: IST-3 trial: 6-month death/dependency = 75% if bNIHSS 6-14 and >95% if bNIHSS ≥15.

- IV tPA pts ≥80 yrs:
  - SITS-ISTR/VISTA (n=2235; bNIHSS, 14): >2/3 dead/dependent at 3-months.
  - IST-3: 72.7% dead/dependent at 6-months.
IAT in the Elderly Revisited:

Hypothetical Outcomes in Young vs. Elderly:
Absolute Benefit vs. Treatment Effect Size

<80 years  ≥80 years

Treatment  Control
IAT in the Elderly Revisited:

- Post-IAT outcomes in pts >80 years is undoubtfully worse vs. younger pts.

- However, given the extremely poor natural history of non-reperfused LVOS in the elderly it is likely that IAT has a larger treatment effect size in patients >80 years than in any other age group.

- Most of the currently published data is based on uncontrolled case series and have inadequately used absolute outcomes rather than treatment effect size as the metric to measure IAT success in the elderly.

- MR CLEAN trial: pts >80 yrs had twice the treatment effect of the younger patients (acOR 3.24 95%CI[1.21-8.62] vs. acOR 1.6 95 CI[1.13-2.27]).

- If compared to historical controls from the SITS-ISTR/VISTA and IST-3 trials our IAT data is similarly suggestive of a high treatment effect in the elderly patient despite overall worse outcomes when compared to younger patients.
Refining the Therapeutic Window for Acute Reperfusion Therapy
Collaterals vs. Time:

- **69 y/o F NIHSS: 23**
- Head CTA/Head CT
- Time to Reperfusion (TICI 3): <3h
- 90-Day mRS: 4

- **67 y/o F NIHSS: 20**
- Head CTA/Brain MRI
- Time to Reperfusion (TICI 2b): >12h
- 90-Day mRS: 2 (NIHSS: 4)
Different Brains Have Different Time Profiles!

The pace of stroke progression appears to be highly variable and is likely dependent of multiple factors other than the duration and intensity of ischemia including:

- Collateral flow (via Circle of Willis and/or leptomeningeal collaterals)
- Ischemic preconditioning
- Cerebral perfusion pressure
- Cerebral blood volume
- Serum glucose
- Body temperature
- Oxygen delivery capacity
“In patients experiencing a typical large vessel acute ischemic stroke, 120 million neurons are lost each hour.”

Jeff Saver, 2006
Temporal Distribution of Stroke Volumes and Clinical-Diffusion Mismatch in Proximal Arterial Occlusions

- 132 consecutive pts with bNIHSS ≥8 + PAO + DWI ≤8 hours from stroke onset:
  - Age, 66±16.8 years; 57% females;
  - Baseline NIHSS 17.5±5.3;
  - Occlusion site:
    - MCA-M1: 64%
    - Intracranial-ICA: 29%
    - Tandem, 5%
  - TSO to DWI, 269.5±105.48 min
  - DWI volume: 46.7±54.8 cc (range, 0.19-436.1) and 63 (46.7%) patients had Clinical-DWI Mismatch
  - No significant changes in age, gender, bNIHSS, or occlusion site amongst the different time quartiles.
  - Median infarct volume (cc) increased (quartile #1=8.5; #2=30.1; #3=38.5; #4=29.4) and the chances of having a CDM decreased (p<0.0001) across the different time quartiles.

- Poor correlation between DWI volume and TSO to MRI (R-square=0.031, Figure)
- Significant proportion of the patients still had a CDM at later time epochs:
  - #1=91.1%[20/22];
  - #2=47.8%[11/23];
  - #3=34.4% [21/61];
  - #4=42.3%[11/26]).
Initial DWI Growth Rate in DEFUSE 2 Patients with M1 Occlusions
Initial DWI Growth Rate in DEFUSE 2 Patients with M1 Occlusions

Baseline DWI Volume (ml)

Time between Symptom Onset and Baseline MRI (hrs)
Initial DWI Growth Rate in DEFUSE 2 Patients with M1 Occlusions
Oct/31/2014: Acute Left MCA-M1 Occlusion: Age 74 NIHSS 26
Stroke Onset: 3PM - IV tPA: 4:48PM - CTP:4:53PM – No IAT

Early Time but Poor Collaterals = Poor Outcome

FAST PROGRESSOR!
Oct/31/2014: Acute Left MCA-M1 Occlusion: Age 74 NIHSS 26
Stroke Onset: 3PM - IV tPA: 4:48PM - CTP:4:53PM – No IAT

Tmax MAPS = Collateral Strength = Time to Reperfuse

Perfusion (Tmax>10.0s) volume: 72.3 ml
Perfusion (Tmax>8.0s) volume: 85.3 ml
Perfusion (Tmax>6.0s) volume: 107.9 ml
Perfusion (Tmax>4.0s) volume: 192.1 ml

Perfusion (Tmax>10.0s) volume: 91.8 ml
Perfusion (Tmax>8.0s) volume: 101.4 ml
Perfusion (Tmax>6.0s) volume: 118.6 ml
Perfusion (Tmax>4.0s) volume: 15 ml
Oct/31/2014: Acute Left MCA-M1 Occlusion: Age 75 NIHSS 24
Last Seen Well: 8PM – No IV tPA - CTP: 11:40AM – IAT: 11:55AM

Late Time but Good Collaterals = Good Outcome

SLOW PROGRESSOR!
Oct/31/2014: Acute Left MCA-M1 Occlusion: Age 75 NIHSS 24
Last Seen Well: 8PM – No IV tPA - CTP: 11:40AM – IAT: 11:55AM

Tmax MAPS = Collateral Strength = Time to Reperfuse
Oct/31/2014: Acute Left MCA-M1 Occlusion: Age 75 NIHSS 24
Last Seen Well: 8PM – No IV tPA - CTP: 11:40AM – IAT: 11:55AM

IAT: 9F BCG + PTAS + 1 Pass Stentriever with Navien 072
DEFUSE 2 - Target Mismatch

90-days mRS

- Reperfusion
  - ≤6h R+ (N=22)
    - 0 to 2: 59%
    - 3 to 4: 27%
    - 5 to 6: 14%
  - ≤6 hours
- No reperfusion
  - ≤6h R- (N=14)
    - 0 to 2: 29%
    - 3 to 4: 29%
    - 5 to 6: 43%
## DEFUSE 2 – Lesion Growth

<table>
<thead>
<tr>
<th>Target Mismatch With Reperfusion</th>
<th>≤6 hrs (N=20)</th>
<th>&gt;6 hrs (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Growth; mL (IQR)</td>
<td>41 (2-73)</td>
<td>26 (7-67)</td>
</tr>
</tbody>
</table>

* 5 day FLAIR volume – baseline DWI volume
**DEFUSE 2 – Lesion Growth**

**Late Treated Patients**

<table>
<thead>
<tr>
<th>Target Mismatch &gt;6 hrs</th>
<th>Reperfusion (N=22)</th>
<th>No Reperfusion (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Growth; mL (IQR)</strong></td>
<td>26 (7-67)</td>
<td>108 (45-185)</td>
</tr>
<tr>
<td><strong>p=0.005</strong></td>
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</table>

* 5 day FLAIR volume – baseline DWI volume
Imaging-Based Endovascular Therapy for Acute Ischemic Stroke due to Proximal Intracranial Anterior Circulation Occlusion Treated Beyond 8 Hours From Time Last Seen Well

OUTCOMES = COLLATERALS TIME

Methods—We conducted a multicenter retrospective review of consecutive patients meeting the following criteria: (1) acute proximal intracranial anterior circulation occlusion; (2) endovascular treatment initiated >8 hours from time last seen well; and (3) treatment selection based on MRI or CT perfusion imaging.

Results—Two hundred thirty-seven patients were identified (mean age, 63.8 ± 16 years; mean baseline National Institutes of Health Stroke Scale, 15 ± 5.5; mean time last seen well to treatment, 15 ± 11.2 hours; male gender, 46%). Successful revascularization was achieved in 175 of 237 (73.84%) patients. Parenchymal hematoma occurred in 21 of 237 (8.66%) patients. The 90-day mortality rate was 21.5% (51 of 237). The rate of good outcomes was 45% (100 of 223) in the 223 patients with available modified Rankin Scale data at 90 days or time of hospital discharge. In multivariate analyses, age (OR, 0.96; 95% CI, 0.94 to 0.98; P = 0.002), admission National Institutes of Health Stroke Scale (OR, 0.93; 0.87 to 0.98; P = 0.016), and successful revascularization (OR, 4.32; 1.99 to 9.39; P < 0.0001) were identified as independent predictors of good outcomes.

Conclusions—Endovascular therapy can be instituted with acceptable safety beyond 8 hours from time last seen well when selection is based on advanced neuroimaging. Successful revascularization is significantly associated with higher rates of good outcomes. The benefit of this approach compared with standard medical therapy should be assessed in a prospective randomized trial. (Stroke, 2011; 42:2206-2211.)
Thanks to the MR CLEAN, ESCAPE, SWIFT PRIME, THERAPY, REVASCAT, EXTEND-IA, THRACE… Investigators and above all the Patients!

It's a beautiful day
Skeptics fall, you feel like
It's a beautiful day
Don't let that clot get away

It is the DAWN of a New Era!
Thank you for your attention!
The Future of Imaging for Endovascular Stroke Therapy
Outcomes After Reperfusion

Outcomes $= \text{Collaterals} \times \text{Time}

↑ Time to Reperfusion $= \downarrow$ Good Clinical Outcome
12% RR $\downarrow$ for every 30-min delay

↑ Time to Treatment $= \uparrow$ Basal Ganglia ICH
11% RR $\uparrow$ for every 10-min delay
Raychev R et al. ISC 2012
Opportunities to Shorten Times To Reperfusion: IMS-III Time Intervals

We have to bypass the Emergency Room and CT Suite!
Why We Will Be Able Bypass the Emergency Room and CT Suite?
Why We Will Be Able Bypass the Emergency Room and CT Suite?

A prospective, multicenter pilot study investigating the utility of flat detector derived parenchymal blood volume maps to estimate cerebral blood volume in stroke patients

David Fiorella,1 Aquilla Turk,2 Imran Chaudry,2 Raymond Turner,2 Jared Dunkin,1 Clemente Roque,1 Marily Sarmiento,3 Yu Deuerling-Zheng,3 Christine M Denice,1 Marlene Baumeister,1 Adrian T Parker,2 Henry H Woo1

Conventional CTP-CBV

Flat detector-parenchymal blood volume (FD-PBV)
Reperfusion Therapy: Refining “Time is Brain”?

Lost per minute

Neurons: $1.9 \times 10^6$
Synapses: $14 \times 10^9$
Myelin fibers: 7.5 miles


“Time is Brain” but….. *variations* according to:

1. Level of Occlusion

2. Individual Anatomy and Physiology (Collaterals)
Level of Occlusion vs. Time
We have known that different levels of occlusion deserve different pathophysiological and therapeutic considerations for a long time... We have just decided to neglect this concept in stroke patients...

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**Level of Occlusion vs. Time:**

- **NSTEMI**
- **ST Elevation Myocardial Infarction (STEMI)**

- **Distal Occlusion or Lacunar Stroke**
- **Proximal Occlusion Stroke**
Level of Occlusion vs. Time:

- Time to Treatment ≠ Time to Reperfusion

- IV thrombolysis pts (bNIHSS 10-14) ≠ IA treated pts (bNIHSS 17-20)

- IV thrombolysis patients
  - Lacunes
  - Distal Occlusions
  - Proximal Occlusions

- IA thrombolysis patients
  - Proximal Occlusions

Figure 3: Model estimating odds ratio for favourable outcome at 3 months in rt-PA-treated patients compared with controls by OTT

Adjusted for age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS measurement.

The rate of infarct growth appears to be dependent on the level of arterial occlusion.

Collateral flow stabilizes the penumbral tissue!
Pathophysiologica\textbackslash{l} consider\textbackslash{a}tions in Large Vessel Occlusion
Physiology is Brain

Penumbra = Ischemia - Infarction
Penumbra = NIHSS - CT/MR image
Penumbra = Clinical - Core Mismatch

Modified from W.T. Yuh and others

Cerebral Blood Flow Thresholds

CBF
ml / 100 gm / min

100
90
80
70
60
50
40
30
20
10

“Penumbra”
“Physiology is Brain”

Region of decreased blood flow

Interruption of blood supply

Fast Growth:
Autoregulation Failure

Slow Growth:
Collateral Failure

↓CBF  ↑CBV  ↑OEF
Individual Anatomy and Physiology vs. Time

Time Window vs. Tissue Window