Objectives
- MRI and CT in recent acute ischemic stroke trials
- Imaging of intracranial atherosclerotic disease
- Future approaches to imaging in trials of novel therapeutic strategies

Framework & Basis for MRI/CT
- Stroke 2013
- Dynamic aspect of cerebral ischemia, artificial separation of phases in ischemic stroke
- Continuum of flow or homeostasis of brain perfusion
- Serial imaging may capture evolution of injury and impact of reperfusion
- Imaging core infrastructure now exists to measure angiographic and tissue biomarkers of ischemia
stroke 2013

- prevention
  - recognition of numerous vascular risk factors from hypertension to glucose intolerance to dyslipidemia
  - embolic source and microvascular disease
  - novel anticoagulants, devices, and other therapies
- optimal medical therapy
- paradoxical omission of hypoperfusion and ischemia
  - role of MRI/CT

time is not brain!

- across population of stroke cases studied from onset to chronic phase, not in a given patient during early phases
- time of symptom onset ≠ time of vascular occlusion
- collaterals prone to failure over time

Early DWI

- 207 stroke patients (mean age 69±17 years, 51% female) from 2004-2012 had DWI with TLKW < 4.5 hours (mean 1.6±2 min)
- DWI lesion volume (median 3.67cc) varied extensively (TLKW-DWI < 1 hour [n=8] 0.40cc (0-93cc), 1-2 hours [n=126] 3.02 (0-265), 2-3 hours [n=78] 2.18 (0-103), 3-4.5 hours [n=95] 6.96 (0-227))
- Negligible correlation (r=0.175, p=0.002) noted for DWI lesion volume and TLKW-DWI time duration
- DWI-negative findings < 4.5 hours occurred in 8.3%
- Malignant strokes (>70cc) were noted in 7.8%
- Older age was associated with DWI-negative strokes (mean 77 vs. 68 years, p=0.013)
  - TLKW-DWI time duration was unrelated to DWI-negative strokes, yet malignant stroke was more common later (p=0.009)
- Majority of malignant strokes on DWI had TLKW during daytime
imaging perspective on time

flow determines time
- If collaterals compensate for arterial occlusion or stenosis, symptoms may be negligible or absent
- Pace of collateral recruitment may influence the timeline of symptom progression
- Poor collaterals may predispose to impaired reperfusion
  - No reflow
  - Reperfusion injury or hemorrhagic transformation

continuum and homeostasis of flow
- Balance of antegrade flow and collateral perfusion
imaging infrastructure

- serial imaging routinely used in clinical practice
- saga of imaging in stroke trials...
  - secondary to clinical outcomes
  - exploratory or ancillary
  - impact of funding source, cost, implications
  - systematic, prospective versus retrospective
  - imaging insurance on understanding pathophysiology
- ongoing, large-scale imaging core lab activities

FAST-MAG

- Los Angeles and Orange Counties
- Ethnically diverse population 13.3 million
- 69 receiving hospitals
- 333 rescue ambulances
- 3330 paramedics
- > 400 emergency physicians
- >100 neurologists, neurosurgeons

FAST-MAG (n=1470)

- currently enrolled n=1584 (6/18/12)
- age 69 (range 39-95)
- female 42%
- index event diagnosis
  - cerebral ischemia 71.9%
  - intracerebral hemorrhage 24.4%
  - stroke mimic 3.7%
- stroke severity
  - LAMS (prehospital) 4.0 (range 1-5)
  - NIHSS (hospital arrival, after Rx start) 11.4 (range 0-40)
FAST-MAG times (n=1470)

- Stroke onset to study drug (median) 46 mins
- Paramedic arrival on scene to drug (mean) 25 mins
- Paramedic arrival on scene to ED (mean) 35 mins
- Treated within 1 hour of onset 73%
- Treated 1-2 hr after onset 24%

ASPECTS

Initial ASPECTS median 9 (IQR 8-10) to 7 (IQR 4-9) at 24 hrs

FAST-MAG imaging
extending thrombolysis

• intravenous thrombolysis – early and late
• baseline imaging patterns predict response
• revascularization – recanalization and reperfusion
• serial imaging of thrombolysis
• hyperperfusion and hemorrhage

early and late – time matters?

Key Results of the DEFUSE Study

• **Target Mismatch** pattern (49%)
  • Benefit substantially from early reperfusion
• **Match** pattern (15%)
  • No benefit from early reperfusion
• **Small DWI / PWI lesions** (28%)
  • Associated with favorable outcomes
• **Malignant MRI** pattern (8%)
  • Predicts severe ICH following reperfusion
Bayesian PWI – collateral perfusion

ASL & DSC MRI

Permeability – CTP and PWI
defining definitive reperfusion

- reperfusion of downstream tissue
- angiographic measures of TICI and collaterals
- endovascular therapies
- serial imaging of reperfusion injury
- definitive reperfusion with good clinical outcome

DEFUSE-2 Definitions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Mismatch</td>
<td>PWI(Tmax&gt;6s) / DWI ≥1.8 AND DWI &lt;70 ml AND PWI(Tmax&lt;10s) &lt;100 ml</td>
</tr>
<tr>
<td>Reperfusion (PWI criteria)*</td>
<td>&gt;50% reduction in PWI(Tmax&gt;6s) volume at early follow-up</td>
</tr>
<tr>
<td>Reperfusion (DSA criteria)**</td>
<td>TICI 2b or 3 at completion of procedure</td>
</tr>
<tr>
<td>Favorable Clinical Response</td>
<td>≥8 point improvement in NIHSSS at day 30 or NIHSSS of 11 at day 30</td>
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</tbody>
</table>

* in patients with a baseline PWI(Tmax<6s) lesion that is ≤10 ml
** in patients with a major vessel occlusion (TICI 0 or 1) on baseline imaging
TREVO 2 vs. SWIFT: Differences

<table>
<thead>
<tr>
<th>TREVO 2</th>
<th>SWIFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Passes with Device</td>
<td>Up to 3 passes with study device. SWIFT device ≤3 passes unless successful.</td>
</tr>
<tr>
<td>Primary Efficacy Endpoint</td>
<td>Successful Recanalization with Study Device</td>
</tr>
<tr>
<td>Definition of Recanalization</td>
<td>TICI 2a, 2b or 3 (Core Lab 1)</td>
</tr>
<tr>
<td>MRS ≤2</td>
<td>mRS ≤2</td>
</tr>
<tr>
<td>≥8 (OR 4.38, p&lt;0.001)</td>
<td>≥8 (OR 2.64, p=0.006), baseline ASPECTS (OR 1.82, p&lt;0.001), and clot location (more ICA than M2 occlusions, p=0.044)</td>
</tr>
<tr>
<td>Multivariate analyses showed that 24-hour ASPECTS (OR 1.70, p&lt;0.001) and post-TICI 2a or greater was not predictive</td>
<td></td>
</tr>
<tr>
<td>Time to TICI 2a or greater was not predictive</td>
<td></td>
</tr>
<tr>
<td>24-hour ASPECTS score 7 was unrelated to age, gender, or any other clinical parameter other than NIHSS score (median 19 [17-22] vs. 17 [13-20] for ASPECTS &gt;7, p=0.001) and clot location (mean ICA than M2 occlusions, p=0.044)</td>
<td></td>
</tr>
</tbody>
</table>

TREVO 2 vs. SWIFT: Comparisons

<table>
<thead>
<tr>
<th>Intraprocedural</th>
<th>TREVO 2</th>
<th>SWIFT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Revascularization</td>
<td>36.0% (n=88)</td>
<td>32.3% (n=88)</td>
<td>0.229</td>
</tr>
<tr>
<td>NIHSS ≤2 at 90d</td>
<td>85.0% (n=156)</td>
<td>82.1% (n=103)</td>
<td>0.377</td>
</tr>
<tr>
<td>NIHSS ≥4 at 90d</td>
<td>15.0% (n=156)</td>
<td>17.9% (n=103)</td>
<td>0.464</td>
</tr>
<tr>
<td>Liberty at 90d</td>
<td>30.0% (n=58)</td>
<td>30.0% (n=37)</td>
<td>1.000</td>
</tr>
<tr>
<td>NIHSS ≥4 at 90d</td>
<td>20.0% (n=58)</td>
<td>17.2% (n=37)</td>
<td>0.687</td>
</tr>
<tr>
<td>NIHSS ≥4 at 90d</td>
<td>20.0% (n=58)</td>
<td>17.2% (n=37)</td>
<td>0.687</td>
</tr>
</tbody>
</table>

Note: 80% patients needed to be needed to demonstrate a difference in TICI 2-3 of 80% vs. 50% (80% power). 50% patients needed in 30-day mRS 0-4 vs. 40% mRS.

TREVO2 imaging details

- 166/177 cases in TREVO2 were anterior circulation occlusions
- Baseline ASPECTS score ≥7 was unrelated to age, gender, or any other clinical parameter other than NIHSS score (median 19 [17-22] vs. 17 [13-20] for ASPECTS >7, p=0.001) and clot location (mean ICA than M2 occlusions, p=0.044) |
- Univariate imaging predictors of good clinical outcome at day 90 included baseline ASPECTS (OR 1.82, p=0.001), baseline ASPECTS >8 (OR 2.44, p=0.001), collateral grade (OR 1.85, p=0.003), post-procedure TICI (OR 2.11, p=0.001), 24-hour ASPECTS (OR 1.87, p=0.001), and 24-hour ASPECTS >8 (OR 4.68, p<0.01) |
- Time to TICI 2a or greater was not predictive |
- Time to TICI 2a or greater was not predictive |
- Multivariate analyses showed that 24-hour ASPECTS (OR 1.70, p<0.01) and post-procedure TICI (OR 3.49, p=0.003) best predicted good outcome.
SWIFT

- SWIFT: Early Presentation is Associated with Better Collaterals, Smaller Established Infarcts, and Better Clinical Outcomes from Endovascular Recanalization
- Impact of Collaterals on Successful Revascularization in SWIFT
- Serial ASPECTS from Baseline to 24 Hours in SWIFT: A Novel Surrogate Endpoint for Revascularization in Acute Stroke

Serial ASPECTS as a Novel Endpoint

ASPECTS change from 8 at baseline to 3 at 24 hrs

stenosis or flow?

- Intracranial atherosclerosis in recent ischemia
- Flow patterns that predict outcome
- Homeostasis of flow
  - TICI/collaterals
  - Fractional flow reserve (FFR)
  - Arteriogenesis and shear stress
  - Hemorrhage
- Computational fluid dynamics (CFD)
CBV gradients, not delay alone...

flow, not % stenosis – WASID

SAMMPRIS – perfusion & SIT

- **Medical**
  - partial TICI/partial collaterals (5/25 (20.0%))
  - complete TICI/partial collaterals (1/95 (1.1%))
  - partial TICI/complete collaterals (0/66 (0%)), p<0.001

- **Stenting**
  - partial TICI/partial collaterals (11/46 (23.9%))
  - complete TICI/partial collaterals (9/93 (9.7%))
  - partial TICI/complete collaterals (0/51 (0%)), p<0.001
CFD of shear stress, arteriogenesis

<table>
<thead>
<tr>
<th>Different Between Angiogenesis and Arteriogenesis</th>
<th>Arteriogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Formation of new capillaries by sprouting</td>
</tr>
<tr>
<td>Source</td>
<td>Im-riceptor expression</td>
</tr>
<tr>
<td>Location</td>
<td>Lower leg</td>
</tr>
<tr>
<td>Origin</td>
<td>Hemo-vascular</td>
</tr>
<tr>
<td>Region</td>
<td>Lower leg</td>
</tr>
<tr>
<td>Cellular mechanism</td>
<td>Vascular mimicry of lymphatic vessels</td>
</tr>
<tr>
<td>Formation time (in weeks)</td>
<td>1-3</td>
</tr>
<tr>
<td>Increased shear stress</td>
<td>&gt; 8</td>
</tr>
</tbody>
</table>

collaterals & hemorrhage in AIS

SAMMPRIS – reperfusion hemorrhage

- Medical
  - ICH within 30 days occurred in 0/186 (0%) subjects

- Stenting
  - Partial TICI/partial collaterals (7/46 (15.2%))
  - Complete TICI/partial collaterals (1/43 (1.1%))
  - Partial TICI/complete collaterals (0/51 (0%), p<0.001)
conclusions

- framework for MRI and CT in acute stroke trials
- imaging of intracranial atherosclerotic disease
- future approaches to imaging in trials of novel therapeutic strategies