Endovascular Therapy for Acute Ischemic Stroke
The new Standard of care for acute large vessel occlusion

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FINANCIAL DISCLOSURE:
- No relevant financial relationship exists
Public Health Impact of Stroke

- Estimated 700,000 strokes occur each year.
- Every 45 seconds, someone in the U.S. has a stroke.
- Stroke is 4th leading cause of death
- **Stroke is leading cause of long-term care disability.**
- 5 million Americans currently living with effects of stroke.
- AHA stroke calculated costs ~ $58 billion in 2006.
- The cost of stroke will double by 2030
Projected number of strokes in US: 2002 - 2025
Stroke by age group
North Dakota State Stroke registry

[Bar chart showing the percentage distribution of stroke cases by age group.]

- <18: 0.1%
- 18-45: 3.8%
- 46-65: 26.1%
- 66-85: 49.3%
- >85: 19.1%
- Unknown: 1.6%
Types of stroke
Types of stroke

- **Ischemic stroke (Blockage)**
  Caused by blockage of a blood vessel in the brain
  80%

- **Hemorrhagic stroke (Bleeding)**
  Caused by burst or a leaking blood vessel in the brain
  20%
Ischemic stroke
Warning Signs of Stroke

A. Numbness on one side
B. Loss of speech or comprehension
C. Unsteady gait
PATHOPHYSIOLOGY
ACUTE STROKE

CBF *

- 55 cc/100 gm/min → Normal flow
- 20 cc/100 gm/min → Reversible symptoms
- <10 cc/100 gm/min → Irreversible damage

STROKE PATHOPHYSIOLOGY (REVERSIBLE INJURY)

- Hemodynamic derangement → low O2 to neurons

- Failure of aerobic respiration and Na/K pump dysfunction

- Cytotoxic edema- Na and H2O flow into cell (cell dysfunction, not destruction)

STROKE PATHOPHYSIOLOGY (IRREVERSIBLE INJURY)

- Ca into cell (Beginning of Irreversible cell injury) → Self-destructive lysosomal enzymes, and apoptotic mechanisms
- 3-4 hrs post ischemia, BBB compromised and plasma proteins released into extracellular spaces → Vasogenic edema
- Cytokines and increased expression of adhesion molecules → phagocytosis and gliosis (new fibrotic tissue)

PATHOLOGICAL CHANGES WITH TIME

ACUTE STROKE

CBF *

- 55 cc/100 gm/min $\rightarrow$ Normal flow
- 20 cc/100 gm/min $\rightarrow$ Reversible symptoms
- $<$10 cc/100 gm/min $\rightarrow$ Irreversible damage

ISCHEMIC PENUMBRA
ISCHEMIC PENUMBRA

Described in 1981*

“ischemic tissue potentially destined for infarction but not yet irreversibly injured and the target of acute therapies.”**

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PENUMBRA
DETERMINING FACTORS

- The duration of ischemia ("time is brain")
- The availability of collateral circulation
- The magnitude and rapidity of the reduction of flow
PENUMBRA IS THE TARGET OF ACUTE STROKE THERAPY

• The goal of acute stroke therapy is to save the penumbra
PATIENT SELECTION

< 3 Hrs

> 3 Hrs

Early time is surrogate marker for penumbra

Ralph Sacco, MD. Acute Stroke Therapy, 2009
CTP: EXAMPLES
HOW TO USE THIS KNOWLEDGE?
STRATEGIES OF ACUTE STROKE THERAPIES

1- Restore the Flow
   - Revascularization
   - Blood pressure
   - Avoid any increase in ICP

2- Neuroprotection
   - Avoid hyperglycemia/hypoglycemia
   - Avoid and treat fever
   - Neuroprotectant (NXY-059, Indomethacin, Mg, hypothermia...)

[Image of a waterfall]
REVASCULARIZATION TECHNIQUES
IV Thrombolytics (clot busting medications)

- FDA approved in 1995
- Standard of care for ischemic stroke for patients presenting within 3 hours of acute ischemic stroke
- Can be used up to 4.5 hours in certain patients.
- Within 90 minutes, Odd ratio for improvement
  \[ OR = 4.43 \] (patient is 4 times more likely to improve)
Interventional Therapy (Endovascular)
Angiography suite
Intra-arterial Thrombolysis
Endovascular therapies for acute ischemic stroke

• Mechanical Thrombectomy
  – Merci
Endovascular therapies for acute ischemic stroke

- Mechanical Thromboaspiration
  - Penumbra aspiration system
Endovascular therapies for acute ischemic stroke

- **Mechanical Thrombectomy**
  - Solitaire FR
Acute Stroke Case

- 52 yo M h/o high cholesterol
- 2 weeks of severe coughing
- Presented with a left middle cerebral artery (MCA) stroke syndrome.
- NIHSS 19.
- Unknown onset. Last known well 4.5 hours.
Acute Stroke Case

- CT perfusion scan demonstrates penumbra, suspected region of salvageable tissue.
Acute Stroke Case

Dense left MCA sign
Acute Stroke Case
Acute Stroke Case
Acute Stroke Case
Acute Stroke Case
Acute Stroke Case

• The following morning patient had improved to minimal aphasia, dysarthria, and right arm pronator drift.
• NIHSS = 3
Endovascular therapy for acute ischemic stroke

53 year-female presented to Essentia Health-Fargo emergency room with severe acute ischemic stroke, severe aphasia and right sided hemiplegia, NIHSS 22 (severely disabled with inability to speak or move her right arm and leg)

Received IV tPA (clot busting treatment) and endovascular therapy (using catheter techniques)

Patient was completely back to normal with very mild right arm weakness when she was discharged from the hospital with NIHSS of 1.
Latest Stroke Trials

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

• Results of the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

Design

• Multicenter (16 Centers in Netherlands)
  – Prospective, randomized trial, open label treatment
  – Blinded assessment of functional outcome at 90 days
  – Blinded assessment of neuro-imaging at baseline and follow-up
• Blinded, web-based, 1:1 randomization
  – Intra-arterial treatment (IA thrombolysis, mechanical treatment or both) plus usual care (could include IV tPA)
  – Usual care alone (control group)
Design

• Inclusion Criteria
  • Acute ischemic stroke, Age ≥18, NIHSS ≥2
  • Intracranial anterior circulation occlusion (confirmed by CTA)
  • Initiation of IA treatment within 6 hours from onset
Patients were randomized 1:1

Baseline CT, CTA
N=502

Randomized

Intervention
N=196

Control
N=267

Received Therapy

*Actual IA Therapy was performed in 196 of 233 pts

End of Follow Up

Results

- Main device: Stent retriever
- NIHSS average at presentation
  - Intra-arterial: 17
  - Control: 18
- Vessel involved
  - M1 in > 60%
  - Distal ICA > 25%
Vessel recanalization

Recanalization on CTA after 24 Hours

Control (68/207): 33%

Intervention (141/187): 75%

* Slide courtesy of Stryker 2015
<table>
<thead>
<tr>
<th>Historical Approach to Dichotomized Modified Rankin Scale Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0</strong></td>
</tr>
<tr>
<td>No symptoms</td>
</tr>
<tr>
<td>Able to carry out all usual activities, despite some symptoms</td>
</tr>
</tbody>
</table>

**SUCCESS** | **FAILURE**
Results

![Bar chart showing Modified Rankin Scale Score distribution between Intervention and Control groups.]

- **Intervention (N=233):**
  - Score 0: 3 patients
  - Score 1: 9 patients
  - Score 2: 21 patients
  - Score 3: 18 patients
  - Score 4: 22 patients
  - Score 5: 6 patients
  - Score 6: 21 patients

- **Control (N=267):**
  - Score 0: 6 patients
  - Score 1: 13 patients
  - Score 2: 16 patients
  - Score 3: 30 patients
  - Score 4: 12 patients
  - Score 5: 22 patients

**No symptoms** to **Death** along the x-axis.
Conclusion

• In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe.

• This treatment leads to a clinically significant increase in the functional independence in daily life by 3 months, without an increase in mortality.
ESCAPE

• Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times
Design

• Methods:
  – 22 centers in Canada, US, Korea, UK and Ireland
  – Randomized, open-label with blinded outcome evaluation, parallel group trial
    • *Intervention:* Endovascular mechanical thrombolysis with an approved approach/device (use of retrievable stents and balloon guide catheters recommended)
    • *Control:* Guideline-based standard of care (IV tPA if <4.5 hrs / stroke unit care)
Inclusion Criteria

- Acute ischemic stroke
- Age ≥ 18 years
- Last-seen-well time to randomization < 12 hours
- ASPECTS >5
- Baseline NIHSS >5 at time of randomization
- Good functional status: pre-stroke modified Barthel Index ≥95, not living in a nursing home; fully independent
- Confirmed symptomatic intracranial occlusion based on CTA in anterior anatomy (Carotid T/L, M1, 2 or more M2’s not including the anterior temporal artery)
- Moderate to good collaterals on CTA
- Endovascular treatment can be initiated within 60 minutes of baseline NCCT with target CT to first recanalization of 90 minutes
Patients were randomized 1:1

Randomized
N=316

Intervention
N=165

+ IV tPA
N=120

No IV tPA
N=45

Control
N=150

IV tPA
N=118

No IV tPA
N=32

Revascularization

Intervention TICI 2b/3
72.4%

Control mAOL 2-3 (at 2-8h CTA)
31.2%

* Slide courtesy of Stryker 2015
Results

Modified Rankin Scale Score

A  Overall

Control (N=147)

Intervention (N=164)

Patients (%)
Conclusions

• Endovascular thrombectomy is a safe, highly effective procedure that saves lives and dramatically reduces disability WHEN:
  – Patients are carefully selected by imaging to identify proximal occlusions and exclude large core and exclude patients with absent collaterals

M Goyal et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. NEJM published on February 11, 2015
SWIFT PRIME

• Solitaire FR With the Intention For Thrombectomy as PRIMary Endovascular treatment for acute ischemic stroke
Design

• Methods:
  – Randomized, open-label with blinded outcome evaluation, parallel group trial
    • Intervention: IV tPA with Solitaire FR Device
    • Control: IV tPA alone
  – 39 enrolling sites in the USA and Europe
Inclusion Criteria

- Acute ischemic stroke
- Age 18-80
- Pre-stroke mRS ≤ 1
- ASPECTS ≤ 6
- Baseline NIHSS 8-29 at time of randomization
- Initiation of IV tPA within 4.5 hours of onset of stroke
- CTA or MRA confirmation of large vessel occlusion in ICA, M1 segment of MCA or carotid terminus
- Endovascular treatment can be initiated within 6 hours of onset of stroke symptoms and within 90 minutes from CTA/MRA to groin puncture
Patients/Randomization

Baseline CTA
N=196

Randomized

Intervention
N=87

Control
N=98

Received Therapy

Modified Intention to Treat

Results of the SWIFT PRIME Trial were presented by Dr. Jeffrey Saver at the International Stroke Conference in Nashville, TN on Wednesday, February 11, 2015.
Successful Reperfusion* (%≥90% reperfusion) at 27 hours

OR: 7.11 (95% CI: 3.03 to 16.70)

* Reperfusion measured by reperfusion ratio assessed by core lab: reperfusion volume at 27 hrs + hypoperfusion lesion volume (Tmax > 6s) at baseline

Results of the SWIFT PRIME Trial were presented by Dr. Jeffery Saver at the International Stroke Conference in Nashville, TN on Wednesday, February 11, 2015.

* Slide courtesy of Stryker 2015
Result

Score on Modified Rankin Scale

No symptoms → Death

Stent Retriever + Intravenous t-PA (N=98)
- 0: 17
- 1: 26
- 2: 17
- 3: 12
- 4: 15
- 5 or 6: 12

Intravenous t-PA (N=93)
- 0: 9
- 1: 11
- 2: 16
- 3: 17
- 4: 22
- 5 or 6: 26
Conclusions

• In AIS patients with confirmed large vessel anterior circulation occlusions treated with IV tPA, rapid treatment with the Solitaire stent retriever lessens post-stroke disability over the entire outcome range and increases the proportion of patients who are alive and independent 3 months after stroke.

• For every two and a half patients treated, one more patient has a better disability outcome.

• For every four patients treated, one more patient is independent at long term follow up.
EXTEND-IA

• A randomized controlled trial of endovascular thrombectomy after standard dose intravenous t-PA within 4.5 hours of stroke onset utilizing dual target imaging selection

B.C.V. Campbell et. al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. NEJM published on February 11, 2015
Rational and Methods

• Rational:
  – To select patients with the best chance of benefit from reperfusion (“Dual Target”)
    • Proven major vessel occlusion AND
    • Salvageable tissue with ischemic core <70mL (CT perfusion)
  – Treat as fast as possible (no waiting to assess tPA “failure”)
  – Use the most effective device (stent retriever)

• Methods:
  – Randomized, open-label with blinded endpoint (PROBE) design
    • Intervention: Stent Retriever (Solitaire FR) + IV tPA
    • Control: IV tPA

B.C.V. Campbell et. al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. NEJM published on February 11, 2015
Inclusion Criteria

• Acute ischemic stroke
• Age $\geq$ 18 years
• Pre-stroke mRS 0-1
• Intra-arterial clot retrieval treatment can commence (groin puncture) within 6 hours of stroke onset.
• Imaging inclusion criteria. Dual target:
  – CTA reveals large artery occlusion in anterior anatomy (ICA, M1 or M2) AND
  – Mismatch - Using CT or MRI with a Tmax $>$6 second delay perfusion volume and either CT-rCBF or DWI infarct core volume.
    • Mismatch ratio of greater than 1.2 and
    • Absolute mismatch volume of greater than 10ml and
    • Infarct core lesion volume of less than 70mL
Patients/Randomization

Randomized
N=70

Intervention
tPA + Endovascular
N=35

Control
tPA only
N=35

IAT never initiated
in 2 pts

Received Angiogram
N=33

mRS Assessment
N=29

B.C.V. Campbell et al. Endovascular Therapy for Ischemic Stroke with Perfusion Imaging Selection. NEJM published on February 11, 2015
Results

Score on Modified Rankin Scale

No symptoms → Death

Endovascular-Therapy Group
- 0: 26
- 1: 26
- 2: 20
- 3: 17
- 4: 3
- 5: 9

Alteplase-Only Group
- 0: 17
- 1: 11
- 2: 11
- 3: 17
- 4: 11
- 5: 20

Patients (%)
Conclusions

• Early mechanical stent thrombectomy after tPA using Solitaire FR led to faster and more complete reperfusion
• In this population selected for vessel occlusion and salvageable tissue this translated to:
  – Improved early neurological recovery
  – Improved functional outcome at 3 months
  – No safety concerns
• tPA + mechanical stent thrombectomy should be the new standard of care
## Trials Summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Imaging Required to Confirm Occlusion Prior to Randomization?</th>
<th>Device(s) Used in Intervention Arm</th>
<th>TICI 2b/3 Revascularization Rate in the Intervention Arm</th>
<th>mRS 0-2</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention Arm</td>
<td>Control Arm</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMS III</td>
<td>No</td>
<td>IA Lytic (138), Merci Retriever® (95), EKOS (22), Penumbra (54), Solitaire FR (5)</td>
<td>38% ICA (n=415)</td>
<td>38.7% (N=214)</td>
<td>0.02 (-0.06 to 0.09)</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>No</td>
<td>Merci Retriever®, EKOS, IA Lytic, Penumbra</td>
<td>24% pen (n=34), 27% nonp (n=30)</td>
<td>21% pen (n=34), 17% nonp (n=30)</td>
<td>26% pen (n=34), 10% nonp (n=20)</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>Yes</td>
<td>97% Stent Retrievers, 2% other Mechanical</td>
<td>58.7% (N=196)</td>
<td>33% (N=233)</td>
<td>19% (N=267)</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Yes</td>
<td>86% Stent Retriever</td>
<td>72.4% (n=156)</td>
<td>53.0% (n=164)</td>
<td>29.3% (n=147)</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>Yes</td>
<td>100% Stent Retriever</td>
<td>88.0% (n=83)</td>
<td>60.2% (n=98)</td>
<td>35.5% (n=93)</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>Yes</td>
<td>100% Stent Retriever</td>
<td>86.2% (n=29)</td>
<td>71% (n=35)</td>
<td>40% (n=35)</td>
</tr>
</tbody>
</table>

* Slide courtesy of Stryker 2015
Essentia Health-Fargo
Stroke and Neurovascular Program
3 Years Outcome Data
IV tPA by year

- FY13: 16
- FY14: 16
- FY15: 43
IV tPA by year

* Projected number for 2015
IV tPA by year and percentage

* Projected number for 2015
tPA times (Mean)

- FY13: 63 minutes
- FY14: 64 minutes
- FY15: 34 minutes
Our Center Experience

- 2012-Current
- 48 Endovascular intervention
- 9.9% of stroke patient received IA therapy
IA Therapy by year

* Projected number for 2015
Endovascular therapy outcome by MRs

- EH
- EXTEND IA
- SWIFT PRIME
- ESCAPE
- MR Clean Endovascular

Legend:
- Blue: 0
- Red: 1
- Green: 2
- Purple: 3
- Teal: 4
- Orange: 5
- Light blue: 6
Thank you