Acute Stroke Intervention

- **IV tPA** has been the standard of care since 1995 (NINDS trial)
  - Can only be administered within 3 hours of stroke onset (or last known well)
  - Used off label in select circumstances up to 4.5 hours after stroke onset
- **Limitations to IV tPA**
  - Time window
  - Eligibility criteria (mostly related to bleed risk)

Acute Stroke Intervention

- Endovascular thrombectomy used off label for many years
  - Used in extended time window – usually up to 6 to 8 hours, in some cases longer
  - Low risk of systemic bleeding
  - Rescue therapy – higher rates of recanalization with large vessel occlusions
  - Examples of devices – MERCI, Penumbra, retrievable stents (“stentriever”)
Acute Stroke Intervention

• Why consider endovascular therapy for acute ischemic stroke?
  – IV tPA is not always effective
  • Poor recanalization rates for large vessel occlusion
  • Pts who do not recanalize tend to have poor outcomes
  – Many pts have contraindications to IV tPA
    • TIME – present outside time window
    • Recent procedure, GI bleed, etc

![Graph showing IV tPA recanalization at one hour (angiographic data)](Del Zoppo et al., Ann Neurol 1993)

![Image of middle cerebral artery branches](Proximal middle cerebral artery (M1) - Middle cerebral artery branches (M2, M3) - Internal carotid artery terminus)
Acute Stroke Intervention

Riedel et al. Stroke, 2011

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Acute Stroke Intervention

Functional Independence

Dependent or bed-bound

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Acute Stroke Intervention

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**Acute Stroke Intervention**

- Intra-arterial thrombolysis
  - 1999 - PROACT II – IA pro-urokinase
    - MCA occlusions
    - Within 6h of stroke onset
    - 40% of treatment group showed improved outcome (mRS ≤ 2) compared to 25% of control group
    - Increased intracranial bleeding rate in rx group (10% vs 3%)
    - No difference in mortality
    - Pro-urokinase not approved by FDA for endovascular treatment of acute ischemic stroke

- 2004 – Interventional Management of Stroke (IMS) trial
  - IV tPA vs. IV tPA + IA tPA
    - Open-label, non-randomized safety trial
      - No difference in mortality, ICH rates, or outcome scores between groups
      - IV tPA as bridging therapy to intra-arterial tPA is safe
  - 2007 – IMS II
    - IV tPA + IA tPA vs. NINDS pts (IV tPA and placebo)
      - Feasibility trial, non-randomized, single-arm
      - Better functional outcome compared to both NINDS groups!
      - No difference in safety endpoints (ICH, mortality)

- Endovascular trials for device approval
  - Single arm, used historical data from prior trials for comparison
    - MERCI/Multi-MERCI
    - Penumbra
    - SWIFT (Solitaire)
    - TREVO
  - FDA 510(k) medical device clearance
    - Easier to obtain than PMA (Pre-marketing approval), which is much more stringent
    - Does the device open up occluded cerebral arteries? Yes/No
    - Endovascular devices are used "off-label" to open arteries when treating acute ischemic stroke
Acute Stroke Intervention

- 2013 – Three randomized, controlled endovascular acute stroke trials
  - IMS III (2006-2012)
    - IV tPA vs. IV tPA + endovascular rx
  - SYNTHESIS (2008-2012)
    - IV tPA vs. endovascular rx alone
    - Standard medical care (may include IV tPA) vs. Standard care + endovascular rx
- No trial showed a benefit in favor of endovascular rx of acute ischemic stroke over the control group

Acute Stroke Intervention

- Several drawbacks:
  - Patient selection
    - Need to establish large vessel occlusion at presentation
      - CTA/MRA not widely available at the time IMS III, SYNTHESIS were initiated
  - Time is brain
    - Long times to treatment with IA therapy (4 to 5.5 hours from onset)
    - Use of newer devices with faster, better recanalization
  - Recruitment issues
    - More effective and speedy recruitment = larger sample size and greater statistical power
    - Competing trials for same patient population
    - Lack of clinical equipoise – desire to use endovascular rx often trumps enrollment into clinical trials

Endovascular Therapy "REEMS" Out Stroke

- REVASCAT
  - June 2015
- ESCAPE
  - February 2015
- EXTEND-IA
  - February 2015
- MR CLEAN
  - December 2014
- SWIFT-PRIME
  - June 2015
MR CLEAN

- Dutch study
- Randomized, controlled, open-label treatment with blinded endpoint assessments
- December 2010 – March 2014
- 16 medical centers (included all stroke centers)
- 500 patients
  - "usual care" (typically IV tPA alone) vs. "usual care" + endovascular rx
- Selection
  - ≥ 18 yo; no upper age limit
  - Proof of anterior circulation artery occlusion on CTA/MRA
  - Ability to initiate IA within 6h of onset
  - NIHSS ≥ 2
- Treatment
  - Endovascular included IA thrombolysis, mechanical thrombectomy, or both

MR CLEAN

RCT of IAT plus usual care vs. usual care.

Similar pre-treatment characteristics

Proximal AOL in the anterior circulation confirmed by CTA < 6 hours from onset

Outcome mRS ≤ 2 at 3 months

260 minutes - average time from start of stroke symptoms to arterial puncture for IAT:
ASPECTS
- Alberta Stroke Program Early CT Score

MR CLEAN
Modified TICI 2b or 3 was 58.7%.
Absolute difference of 13.5% in the rate of functional independence mRS 0-2 in favor of IAT.

TICI Scale
- Thrombolysis In Cerebral Infarction Scale
MR CLEAN

No significant difference in SICH or death.

ESCAPE

Hypothesis – IAT vs standard care in patients with:
1. small core infarct
2. proximal AO and
3. moderate-to-good collateral circulation – CTA multiphase

Stopped for efficacy
EXTEND IA

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection


EXTEND IA

IAT (Solitaire FR) vs usual care
1. Proximal AO (SCA, M1 M2)
2. Ischemic core <70 cc by CTP (Rapid Software)

Australia, New Zealand, 10 centers
Stopped early after 70 patients randomized

EXTEND IA

Reperfusion is % reduction of perfusion lesion volume at 24 hours. Early neurological improvement is NIHSS decrease of 8 or 0-1 at day 3.
All patients received IVT prior to randomization

100% stentriever in the IAT arm

Stopped early for efficacy

39 centers in US and Europe

LVO occlusion confirmed prior to randomization

Rapid Software
REVASCAT

ORIGINAL ARTICLE

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke


REVASCAT

Four centers in Catalonia, Spain
Also stopped for efficacy
• Why do the recent trials show a benefit with endovascular when prior trials have failed to do so?
  – Selection based upon evidence of large vessel occlusion (ICA terminus, M1)
  – Stentriever and ADAPT technique (direct aspiration with large bore catheter)
  – Fast work flow → overall shorter times to intervention
  – High severity stroke
  – More focused, effective recruitment
• What do the recent endovascular trials tell us?
  – TIME IS BRAIN
    • Most trials required groin puncture before 6 hours
    • Short time from stroke onset to groin puncture is associated with higher chances of better outcomes
  – Successful reperfusion is associated with better outcomes

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<th>Summary</th>
<th>Age</th>
<th>NIHSS</th>
<th>ASPECTS</th>
<th>IVT</th>
<th>Year to IAT</th>
<th>GP TICI 2b</th>
<th>Death</th>
<th>SICH</th>
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What do the recent endovascular trials tell us?

- **TIME IS BRAIN**
  - Most trials required groin puncture before 6 hours
  - Short time from stroke onset to groin puncture is associated with higher chances of better outcomes
  - Successful reperfusion is associated with better outcomes

- Endovascular thrombectomy is not riskier than the standard of care (including IV tPA)
  - Similar mortality rates (10-20%)
  - Similar symptomatic ICH rates (up to 6%)

Endovascular thrombectomy is now standard of care for treatment of acute ischemic stroke

- **American Stroke Association 2015 Endovascular Update** recommends endovascular therapy with a stent retriever for patients meeting the following criteria:
  - Prestroke mRS score 0 to 1
  - Acute ischemic stroke receiving IV tPA within 4.5 hours of onset
  - Causative occlusion of the internal carotid artery or proximal MCA (M1)
  - Age ≥ 18 years
  - NIHSS score of ≥ 6
  - ASPECTS of ≥ 6
  - Treatment can be initiated (groin puncture) within 6 hours of symptom onset
• Patients who have unfavorable advanced neuroimaging (perfusion, collateral grade) may not benefit from endovascular rx
• The new guideline recommendations are inclusion criteria (not exclusions) because they don’t address:
  – Patients who are not eligible for IV tPA
  – Patients with a prestroke mRS > 1
  – Patients with “extended” time windows – those who physiologically have minimal infarct even after 6 hours
  – Patients with occlusions of M2 branches, ACA, PCA, basilar or vertebral arteries

• These are smaller subpopulations that may still benefit from endovascular therapy on a case by case basis, and require further study
  – Thus they should still be considered as potential candidates, and should be discussed with a vascular neurologist

• Evaluation and administration of IV tPA should not be delayed in potential endovascular patients!!!
  – Non-contrast head CT
  – CTA/MRA head and neck (should not delay giving IV tPA)
  – Advanced neuroimaging???

• Potential endovascular patients should be transferred to a Comprehensive Stroke Center
  – Discussion with vascular neurologist
  – 24/7 access to vascular neurology, neurosurgery, neurointensivists, neuroradiology, neurointerventionalists
  – Transfer should occur as soon as possible
    • Defer CTA/MRA and further imaging if performing them would delay transfer

Questions?