Endovascular Therapy forStroke
• PROACT II (1999, IA urokinase) first to demonstrate benefit of EST
• Newer trials (including MERCI in 2005) demonstrated vessel recanalization but no clinical benefit
Based on the DOE (Disease Oriented Endpoint) of recanalization, FDA approved devices under 510(K) clearance (doesn’t require evidence of clinical benefit)

Other studies started, but many places started doing the procedures right away
• IMS-III, SYNTHESIS and MR RESUCE published in NEJM – all different, but all negative
• Pro-EST crowd had lots of criticisms of these studies
  o Most used non-con CTs rather than CTA/MRA
  o Time windows were too long
  o Used wrong equipment (MERCI, rather than newer/shinier devices)
    • MERCI recanalized vessels about 2/3 of the time, newer devices around 80% of the time – how big a difference is that?

• No RCT to this point showed improvement in any POE (Patient Oriented Endpoint), only the DOE of vessel recanalization
• MR CLEAN published New Year’s Day 2015 – a big deal
• First RCT to show significant improvement in clinical outcomes with EST (NNT: 7)
• PROBE design (Prospective Randomized Open Label Blinded Endpoint)
• Highly selected pt population
  o Large anterior circ stroke w/large vessel occlusion of ACA, MCA or distal ICA demonstrated by CTA or MRA
  o Intervention w/in 6 hours of symptom onset
• Pts ineligible for one treatment eligible for the others
  o 89% received IV tPA
• No difference in mortality or sICH, BUT 5.6% developed new stroke in new distribution (embolization?) vs 0.4% of control group (NNH: 19)
• 6 other RCTs were underway when MR CLEAN's results were released at ISC in November 2014
• All 6 did interim analyses, stopped early, and sprinted to publish their results

EXTEND-IA
Tiny numbers, great outcomes (NNT 2-5)

ESCAPE
12 hours
NNT 5
- **EXTEND-IA**
  - Only 70 pts, strange outcome measures (3 days, plus another perfusion DOE; 90d mRS was secondary outcome)
  - Intervention begun within 6 hours, completed within 8
  - NNT 2-5 depending on outcome

- **ESCAPE**
  - 12-hour window
  - Used ASPECT scores rather than CTA/MRA
  - Only study to show SS mortality benefit (NNT 11)
  - NNT for 90d mRS 0-2: 5

- **SWIFT PRIME**
  - NNT: 4

- **REVASCAT**
  - 8 hours
  - NNT 6.5
• SWIFT PRIME
  o Required no large ischemic core on perfusion imaging
  o Changed imaging criteria half-way through
  o 90d mRS 0-2: NNT 4

• REVASCAT
  o Site selection: had to be doing ≥60 procedures/year
    • Intrinsic bias towards doing procedures – why would you be when there was no evidence at this point?
  o 8-hour window, no large infarct
  o Pts had to be either ineligible for IV tPA or have CTA-proven lack of recanalization within 30 minutes of tPA
  o 90d mRS 0-2: NNT 6.5

**Therapy**

- Stopped early
- No SS benefit

**THRACE in 2016**

- NNT: 9
- No SS difference in mRS w/ordinal analysis
• THERAPY
  o Stopped after only 108 of planned 692 pts enrolled
  o Trend towards positive but not SS
• THRACE
  o 2nd largest enrollment
  o 90d mRS 0-2: NNT 9 (ordinal analysis of mRS showed no benefit)
• One small/underpowered failed trial and one trial with benefit that is smaller and questionable – first trials not published in NEJM, no fanfare

DAWN
6-24 hours
NNT: 3
• Extended window (6-24h) – includes “wake up strokes”
• Stopped early d/t benefit
• Co-primary endpoints
  o Novel, complicated endpoint positive (?)
  o 90d mRS 0-2: NNT 3
• DEFUSE 3: Stopped early d/t benefit (6-16 hrs; not yet published)
• CRISP: trying to ID pts >6 hrs who will benefit
  o "perfusion target mismatch profile" on CTA
• POSITIVE: 6-12 hrs
Statistical/Methodological Concerns

- All trials after MR CLEAN stopped early (tends to magnify benefit)
  - 2 of the 3 trials closest to completion (also 2 with largest enrollments) had the smallest benefit of all of the trials
- Ordinal analysis used in many of the studies (controversial)
- Intrinsic bias – many of the researchers have been involved in these projects for decades; REVASCAT site selection
- All either fully or partially funded by device manufacturers
- All were open label
- mRS has poor inter-rater reliability
  - Problem with using a subjective measure with poor inter-rater reliability in an open-label trial when you know whether or not you got the “special treatment”
- All compared to tPA alone (no placebo)

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<thead>
<tr>
<th>STUDY</th>
<th>PTS/CENTER/YEAR</th>
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<tbody>
<tr>
<td>IMS-III</td>
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<tr>
<td>SYNTHESIS</td>
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<td>MR RESCUE</td>
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<td>ESCAPE</td>
<td>8.2 (17.3?)</td>
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<td>SWIFT PRIME</td>
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<tr>
<td>REVASCAT</td>
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<tr>
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<tr>
<td>DAWN</td>
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• Only EXTEND-IA told us how many they screened
  o Almost 7800 strokes to enroll 70 (0.9% of strokes eligible; 1/110)
• If you need to treat 7 for one to get benefit (MR CLEAN), that’s 1/770 strokes that will benefit from this therapy
• Would require massive overhaul of EMS and hospital systems, massive costs
  o Every stroke pt would require CTA (~$1000 + dye/radiation)
  o Diverting all stroke pts to centers w CTA/MRA available
• What are the chances hospitals will make this kind of investment (devices, staff, training, on-call interventionalists 24/7) and be happy with one procedure every 2 months?
  o Already was happening at sites chosen for the REVASCAT trial, likely many others
  o Remember negative results of IMS-III, SYNTHESIS, MR RESUCE in pt populations that weren’t highly selected

SUMMARY
• 7 RCTs have demonstrated benefit (NNT: 2-12) of ETS if:
  o Anterior stroke
  o Clot in a large proximal vessel by CTA/MRA
• ETS benefits only 1/~770 stroke patients
• Areas for future study
  o ID middle ground group that could benefit
  o ETS without IV tPA?
  o Extending the window
• Indication creep a huge concern
References/Additional Reading

DING DONG, THE DROUGHT IS DEAD!!!