Overview of new acute stroke trials

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State of stroke care ~ 2011-2012

- Some ischemic stroke patients benefit from intervention / thrombectomy
- Recanalization futile in others
- Improvements in procedural success with use of stentrievers
    - SOLITAIRE™ FR (Covidien, Irvine, CA)
    - TREVO™ (Concentric Medical, Mountain View, CA)
- Clinical trials underway to 'prove' treatment works

Interventional Trials 2013

- IMS3 (Broderick et al)
- MR-RESCUE (Kidwell et al)
- SYNTHESIS (Ciccone et al)

- Neutral results
- Changed practice
- Impacted reimbursement of treatment

Criticisms of these trials

- End point of incomplete perfusion
- Delay in CT to groin puncture/recanalization
- Enrollment bias
- Long enrollment process
- Old technology

Interventional trials 2014-2015

- MR CLEAN (Berkhemer et al)
- ESCAPE (Goyal et al)
- EXTEND-IA (Campbell et al)
- SWIFT-PRIME (Saver et al)
- REVASCAT (Jovin et al)

Commonalities to 2014-2015 trials

- Documentation of vessel occlusion required
- Specified time to treatment
  - Median stroke onset to treatment ~4 hours
- Recanalization endpoint of TICI 2b or 3
- Rapid enrollment of patients
- mRS (modified Rankin Scale) score as primary outcome
- Homogeneity of clinical and radiographic benefit
  - Number needed to treat in single digits

MR CLEAN – <u>M</u>ulticenter <u>R</u>andomized <u>Cl</u>inical trial of <u>E</u>ndovascular treatment for <u>A</u>cute ischemic stroke in the <u>N</u>etherlands

- All patients from the Netherlands
- 6 hour window; <u>any type of mechanical/chemical treatment</u>
- <u>Selection based on vessel imaging</u>
    - CTA/MRA/DSA based selection
    - ICA, ACA, M1, or M2
- Primary outcome: modified Rankin Scale (mRS) score at 90 days
    - Good outcome as mRS of 0-3

MR CLEAN

- 500 patients
- NIHSS 17 (18 controls)
    - 87% treated with IV tPA (91% controls)
- 97% retrievable stents
- Median ASPECTS 9
- TICI 2b/3 59% (24% TICI 3)
- Stroke onset to groin puncture <u>260 min</u>
- Infarct volume at 7 days 49 mL (79 mL in controls)
- Mortality at 30 days: 18.9% vs 18.4% (NS)
- Symptomatic ICH: 7.7% vs 6.4% (NS)

- Number needed to treat for mRS ≤2: 8

MR CLEAN
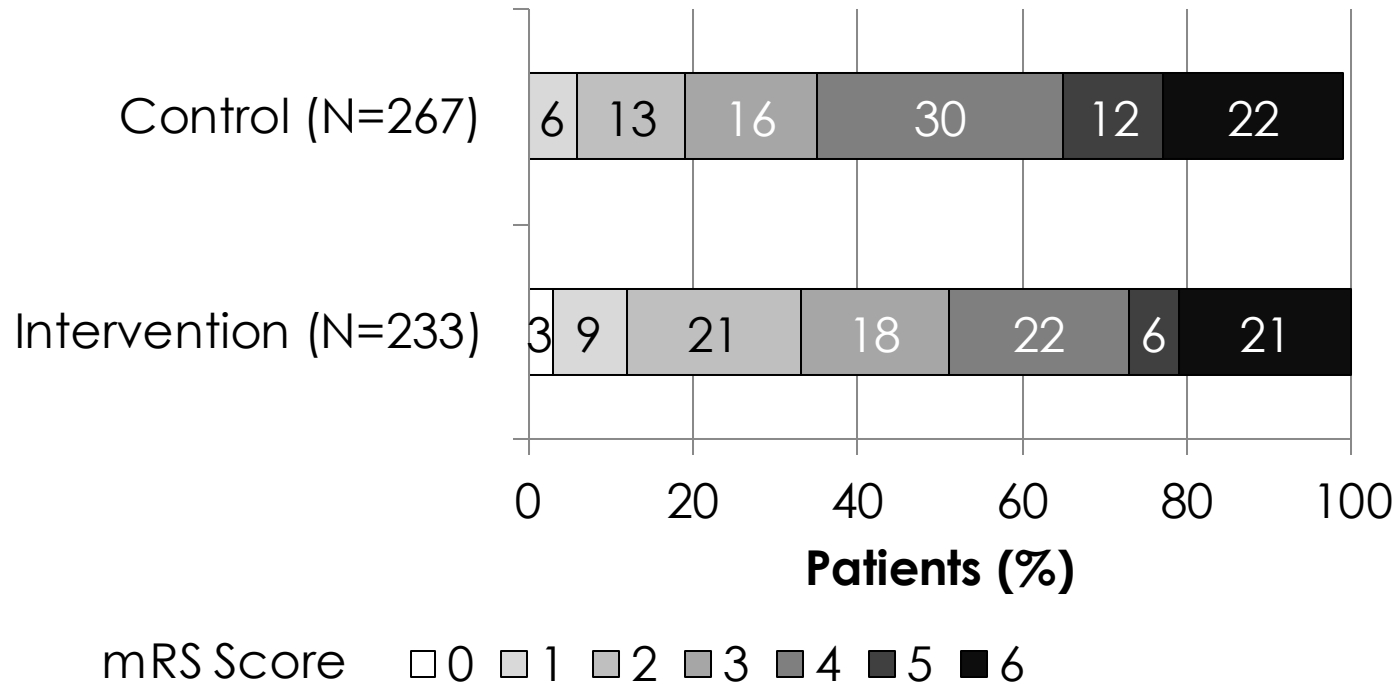
Berkhemer et al, *NEJM*, 2014

ESCAPE – (Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times)
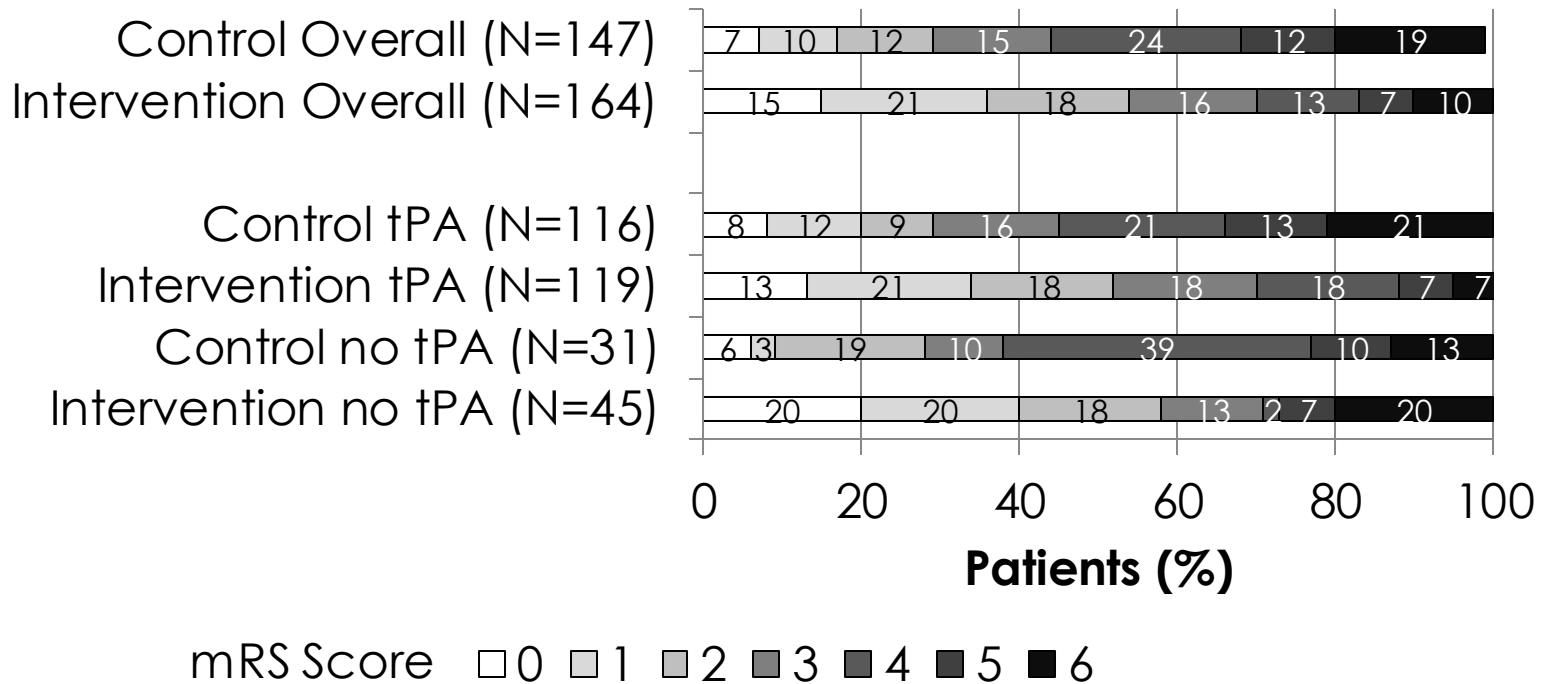
- Primarily based out of Canada
- 12 hour window for enrollment
- CT/CTA (multiphase) based selection
    - ASPECTS score 6 or greater
    - Proximal (ICA and/or M1) occlusion
    - Moderate to good collaterals on CTA
- CT to groin: 60 min; CT to recan: 90 min
- Primary outcome: mRS score at 90 days
- Stopped at (unplanned) interim analysis

ESCAPE

- 311patients (stopped early due to efficacy)
- NIHSS prior to treatment: 16 (17 in controls)
- 75% received IV - tPA
- 86% retrievable stents
- Median ASPECTS 9
- 72% TICI 2b/3 at end of procedure
- Stroke onset to reperfusion 241 minutes
- Mortality 10% vs 19% (p=0.04)
- Symptomatic ICH 3.6% vs 2.7% (NS)

- Number needed to treat for mRS score ≤2: 4
  - 3 for shift in mRS

ESCAPE

Control Overall (N=147)
Intervention Overall (N=164)
Control tPA (N=116)
Intervention tPA (N=119)
Control no tPA (N=31)
Intervention no tPA (N=45)

Patients (%)

mRS Score □0 □1 □2 ■3 ■4 ■5 ■6

Hill et al, *NEJM*, 2015

EXTEND- IA: Extending the Time for Thombolysis in Emergency Neurological Deficits – Intra-Arterial

- Primarily out of Australia
- 6 hour window, tPA alone vs tPA plus IA (Solitaire)
- MRI based selection
  - RAPID software
  - ICA, M1 or M2 occlusion
  - Mismatch with core <70 mL
- Primary outcomes: MRI at 24 hours and early clinical improvement (3 day NIHSS)

EXTEND-IA

- 70 patients total (stopped early due to efficacy)
- NIHSS prior to treatment 17 (13 controls)
- Baseline ischemic core 12 mL; penumbra 106 mL (core 18 mL in controls)
  - 24 hour ischemic core 18 mL (49 mL in controls)
- CT to groin puncture 93 min
- Onset to completion/reperfusion 248 min
- 86% TICI 2b or 3 (48% TICI 3)
- MRI evidence of reperfusion 100% vs 37% (p<0.001)
- Early improvement 80% vs 37% (p<0.001)
- Mortality 9% vs 20% (NS)
- Symptomatic ICH 0% vs 6% (NS)

- Number need to treat for mRS score ≤2: 4
  - 3 for shift in mRS

EXTEND- IA
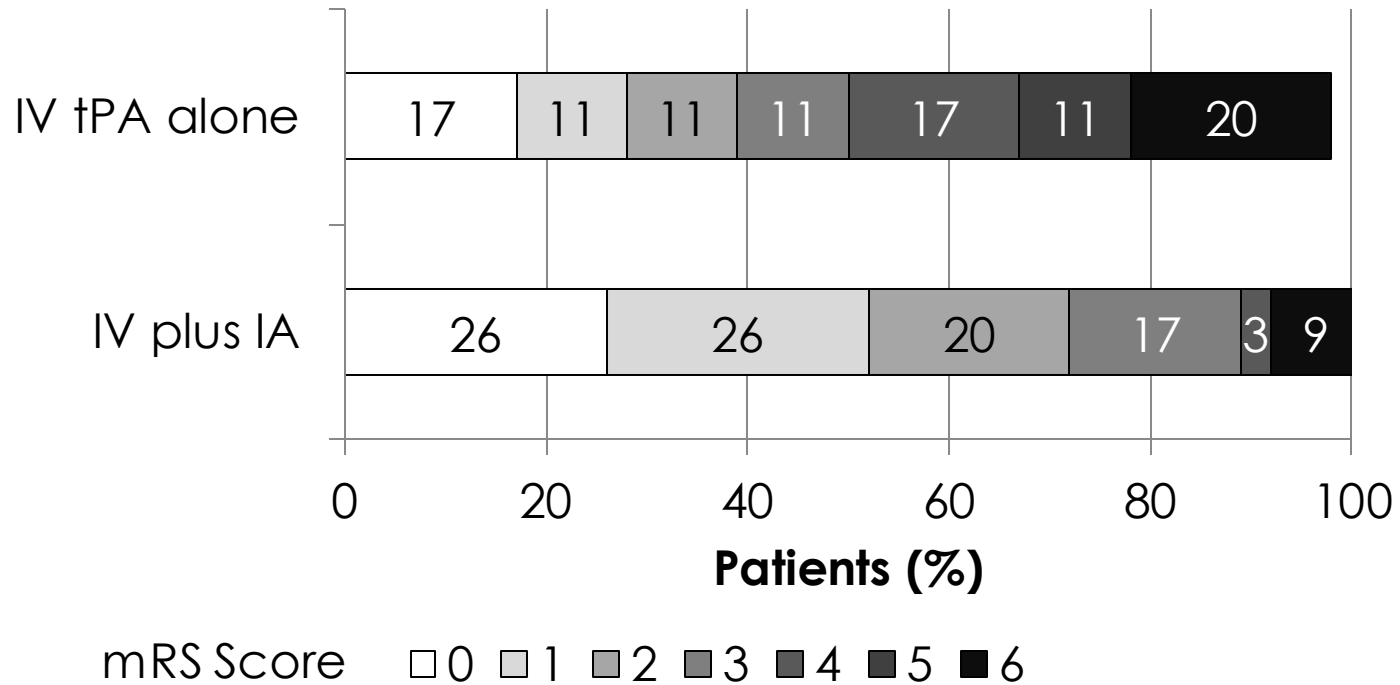
Campbell et al, *NEJM*, 2015

SWIFT-PRIME: <u>S</u>OLITAIRE™ FR <u>W</u>ith the <u>I</u>ntention <u>F</u>or <u>T</u>hrombectomy as <u>PRIM</u>ary <u>E</u>ndovascular Treatment for Acute Ischemic Stroke

- US and European sites
- 6 hour window (to groin puncture); IV tPA and SOLITAIRE vs IV tPA alone
- CTA or MRA confirmation of ICA or M1 occlusion (no cervical carotid occlusion)
- ASPECT score ≥6, <u>core lesion ≤50 mL</u>, target mismatch ratio >1.8

- Primary outcome: mRS at 3 months
  - mRS 0-2 considered good outcome

SWIFT PRIME

- 195 patients (stopped at interim analysis)
- NIHSS prior to treatment 17
- 88% TICI 2b/3 (69% TICI 3)
- CT to groin puncture 57 min
- Onset to stent deployment 252 min
- Mortality at 90 days 9% vs 12% (NS)
- Symptomatic hemorrhage 0% vs 3% (NS)

- Number needed to treat for mRS≤2: 4
    - 2.6 for shift in mRS

SWIFT PRIME
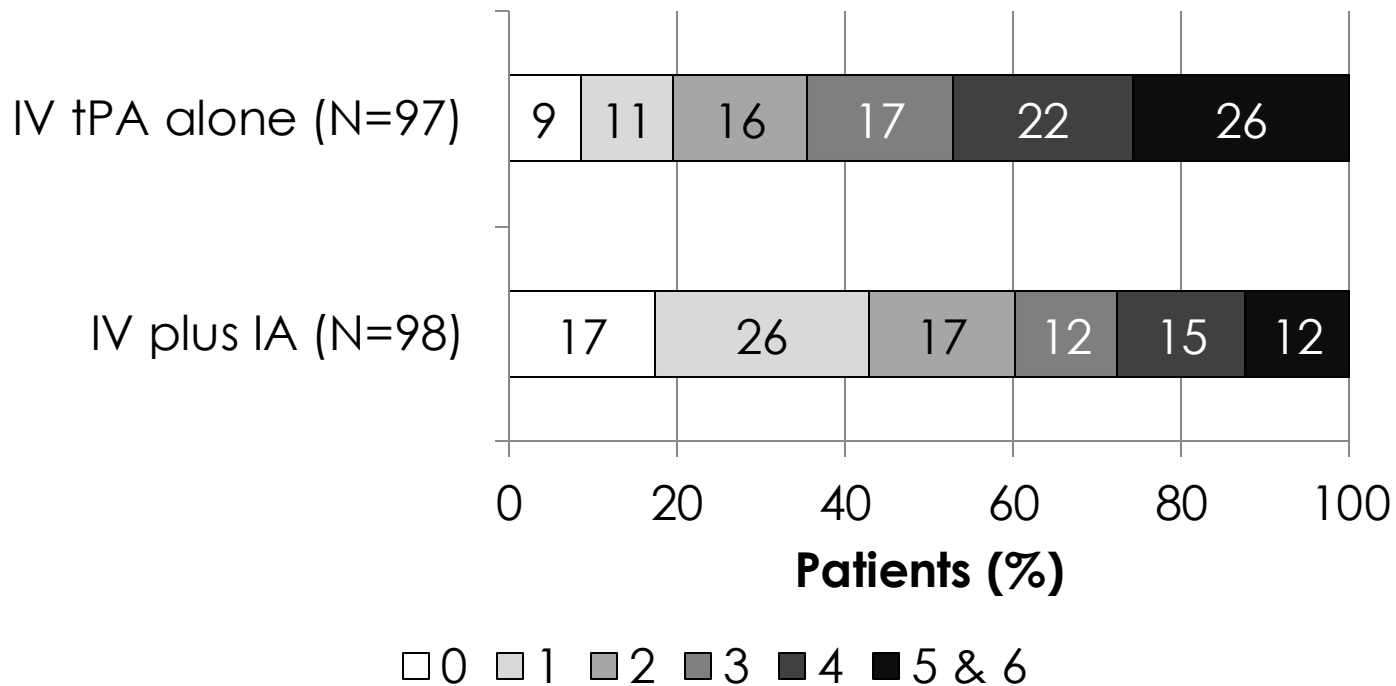
Saver et al, *NEJM*, 2015

REVASCAT: RandomizEd Trial of ReVascularizAtion with Solitaire FR Device vs Best MediCal Therapy in the Treatment of Acute Stroke Due to AnTerior Circulation Large Vessel Occlusion Presenting within 8 Hours of Symptom Onset

- Patients from Catalonia, Spain
- 8 hour window to treatment; best medical therapy +/- Solitaire
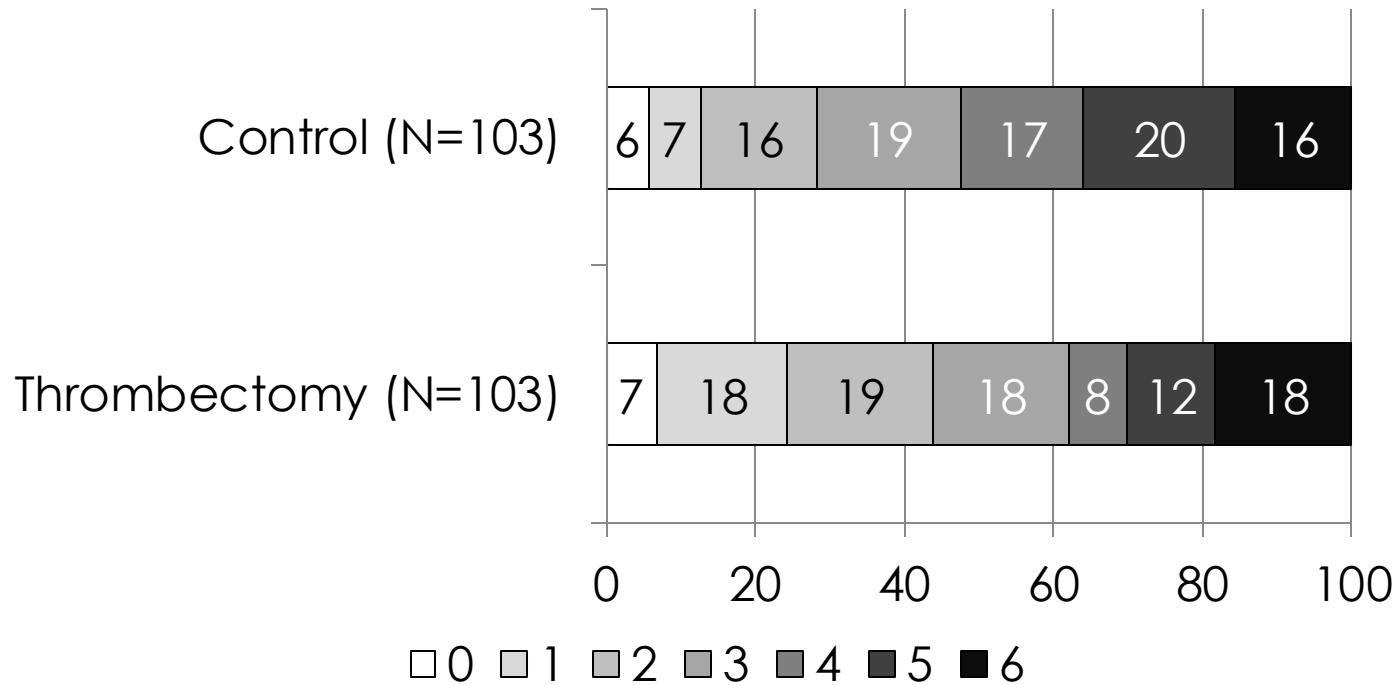- ICA , M1 or M2 occlusion
- ASPECT score ≥7 (CT) or ≥ 6 (MRI)

- Primary outcome: mRS at 3 months

REVASCAT

- 206 patients total; NIHSS prior to treatment 17
- ASPECTS score 7
- 66% TICI 2b or 3 (19% TICI 3)
- CT to groin puncture 77 min*
- Onset to revascularization 355 min
- 24 hour infarct volume 16mL vs 39 mL (p=0.02)
- Mortality at 90 days 18% vs 15% (NS)
- Symptomatic hemorrhage 5% vs 2 % (NS)

- Number needed to treat for mRS ≤ 2: 7

REVASCAT

Control (N=103): 6 | 7 | 16 | 19 | 17 | 20 | 16

Thrombectomy (N=103): 7 | 18 | 19 | 18 | 8 | 12 | 18

Scale: 0 20 40 60 80 100

Legend: □0 □1 □2 □3 □4 ■5 ■6

Jovin et al, *NEJM*, 2015

Summary

Trial	# of Patients	% tPA	ASPECTS (range)	TICI 2b/c	Onset to IA treatment	NNT mRS ≤2
MR Clean	500/233	87	9 (0-10)	59%	260*	8
ESCAPE	311/164	73	9 (6-10)	72%	185*/241‡	4
EXTEND-IA	70/35	100	n/a	86%	210*/248‡	4
SWIFT PRIME	196/98	100	9 (6-10)	88%	224*/252†	4
REVASCAT	206/103	68	7 (6-10)	66%	269*/355‡	7

*: groin puncture
†: stent deployment
‡: recanalization/end of procedure

Summary

- Thrombectomy is efficacious in treating ischemic stroke patients with:
    - Proximal occlusion
    - Favorable imaging profile
    - Recent symptom onset