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Thrombectomy 6 to 24 Hours after Stroke with a Mismatch
between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel, V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim, J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith, D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*

RBWH ICU Journal Club
February 2018
Adam Simpson

THROMBOLYSIS

Reperfusion therapy has become the mainstay of therapy for ischaemic stroke.

Thrombolysis is now well accepted within 4.5 hours.

- Improved chance of favorable outcome / independence.
- More ICH but no 3 month mortality change.
- Increased ICH and mortality if reperfusion beyond 6 hours.

(NINDS, ECASS I, II and III, ATLANTIS A and B and subsequent databases including SITS-ISTR)

DELAYED THROMBOLYSIS

3 – 4.5 hour group at increased risk of ICH.

Therefore further exclusion criteria apply:

Patients >80yo, anti-coagulated regardless of INR, large stroke (NIHSS >25), large stroke volume (>1/3 MCA territory), history of prior stroke or diabetes

Use of perfusion scanning to select for appropriate patients may push this timing out further and evidence for this practice is increasing (Bivard et.al 2015).

THROMBECTOMY

Has become well established with good evidence of benefit if implemented within 6 hours.

Goyal et.al. 2016. Meta-analysis of 5 x RCTs (MR CLEAN, ESCAPE, REVASCAT, SWIFT, PRIME, EXTEND IA)

Thrombectomy vs. standard care of proximal anterior circulation stroke within 12 hours of symptoms onset.

Collated a total of 1287 patients.

Primary outcome was functional independence at 90 days.

OR 2.49 NNT 2.6. (26% in control vs. 46% in treatment)

No difference in mortality or ICH

Majority of good outcomes in the treatment within 6 hours groups

THROMBECTOMY

THRACE: Bracard et.al. 2016: Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke

t-PA within 4 hours (208) **vs.** t-PA within 4 hours PLUS thrombectomy within 5 hours (204)

Outcome was mRS of 0-2 (functional independence) at 3 months.

Control: 42%. Treatment: 53%. **OR 1.55**

No mortality (12% vs 13%) or ICH difference (2% vs 2%)

DELAYED THROMBECTOMY

Response to reperfusion therapy should depend on size of salvageable brain tissue.

‘Tissue window’ vs. ‘time window’

Previous studies have revealed a potential role for detecting salvageable brain tissue that may be amenable to reperfusion (Davalos et.al 2004, Jovin et.al 2011, Lansberg et.al 2015).

Should perfusion studies be used instead of time as a marker for response to reperfusion therapy?

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METHODS

“International, multicenter, prospective, randomized, open-label trial with a Bayesian adaptive-enrichment design and with blinded assessment of end-points”

26 centers in US, Canada, Europe and Australia.

Independent investigators in collaboration with the sponsor
Stryker Neurovascular

METHODS

Patients:

- >18 years old
- CTA or MRA confirmed proximal anterior circulation stroke (intracranial ICA or MCA-1)
- Last known to be well 6 to 24 hours ago
- Mismatch between clinical deficit and infarct on CT or MR perfusion study.

Mismatch between clinical deficit and infarct volume defined according to the following criteria:

A: 80 years or older , NIHSS score >10, stroke volume < 21ml

B: <80, NIHSS >10, stroke volume < 31ml

C: <80, NIHSS >20, stroke volume 31-51ml

METHODS

Randomisation:

1:1 ratio into treatment or control group via central, web-based procedure. Blocks minimization to balance the two groups.

Stratified according to :

- Mismatch criteria: Group A, B and C
- Time interval since last well (6 -12 and 12-24 hours)
- Occlusion site (ICA or MCA)

Blinding:

Open label intervention

Blinding of the outcome investigators

METHODS

Intervention:

- Standard care – as per local guidelines. Included thrombolysis

Plus

- Mechanical thrombectomy with the Stryker Trevo device (retrievable, self-expanding stent)

Control:

- Standard care – as per local guidelines. Included thrombolysis

METHODS

Outcomes:

Primary:

- 1: Utility weighted modified Rankin Scale at 90 days
- 2: Functional independence as defined by mRS of 0-2 at 90 days

Secondary:

1. Early response: Decreased in baseline NIHSS >10 or NIHSS of 0 or 1 by day 7
2. Death of any cause at day 90
3. Infarct volume at 24 hours
4. Recanalization at 24 hours
5. Thrombectomy group only: Recanalization at end of procedure

METHODS

Statistical analysis:

Adaptive design allowing sample size of 150-500.

Interim analysis where trial could be ceased based on pre-determined criteria.

Intention to treat analysis.

86% power to detect an adjusted difference between the two treatment groups in the mean score on Utility-weighted modified Rankin scale of **1.0**

Enrollment ceased at 31 months with just over 200 patients

Interim analysis revealed a predictive probability of superiority of thrombectomy of at least 95%.

RESULTS

Total 206 patients enrolled.

- 107 to thrombectomy – thrombectomy occurred in 105
- 99 to control

Groups reasonably well matched except for a few key differences:

Median infarct: 7.6ml vs. **8.9ml** in control

Median time interval: 12.2hrs vs. **13.3hrs** in control

Thrombolysis: 5% vs. **13%** in control

AF: **40%** vs. 24% in control

Wake up stroke: **63%** vs. 47% in control

Unwitnessed stroke: 27% vs. **38%** in control

Table 1. Characteristics of the Patients at Baseline.*

Variable	Thrombectomy Group (N=107)	Control Group (N=99)
Age — yr	69.4±14.1	70.7±13.2
Age ≥80 yr — no. (%)	25 (23)	29 (29)
Male sex — no. (%)	42 (39)	51 (52)
Atrial fibrillation — no. (%)	43 (40)	24 (24)
Diabetes mellitus — no. (%)	26 (24)	31 (31)
Hypertension — no. (%)	83 (78)	75 (76)
Previous ischemic stroke or transient ischemic attack — no. (%)	12 (11)	11 (11)
NIHSS score†		
Median	17	17
Interquartile range	13–21	14–21
10 to 20 — no. (%)	78 (73)	72 (73)
Treatment with intravenous alteplase — no. (%)	5 (5)	13 (13)
Infarct volume — ml		
Median	7.6	8.9
Interquartile range	2.0–18.0	3.0–18.1
Type of stroke onset — no. (%)‡		
On awakening	67 (63)	47 (47)
Unwitnessed stroke	29 (27)	38 (38)
Witnessed stroke	11 (10)	14 (14)
Occlusion site — no. (%)§		
Intracranial internal carotid artery	22 (21)	19 (19)
First segment of middle cerebral artery	83 (78)	77 (78)
Second segment of middle cerebral artery	2 (2)	3 (3)
Interval between time that patient was last known to be well and randomization — hr		
Median	12.2	13.3
Interquartile range	10.2–16.3	9.4–15.8
Range	6.1–23.5	6.5–23.9
Time from first observation of symptoms to randomization — hr		
Median	4.8	5.6
Interquartile range	3.6–6.2	3.6–7.8

RESULTS

No comment on number of patients screened and rejected from randomisation

No patients completely lost to follow up but:

43 (20%) patients not followed up in person

- phone interviews with patient or caregiver

RESULTS - PRIMARY

1st Primary Outcome (UWmRS):

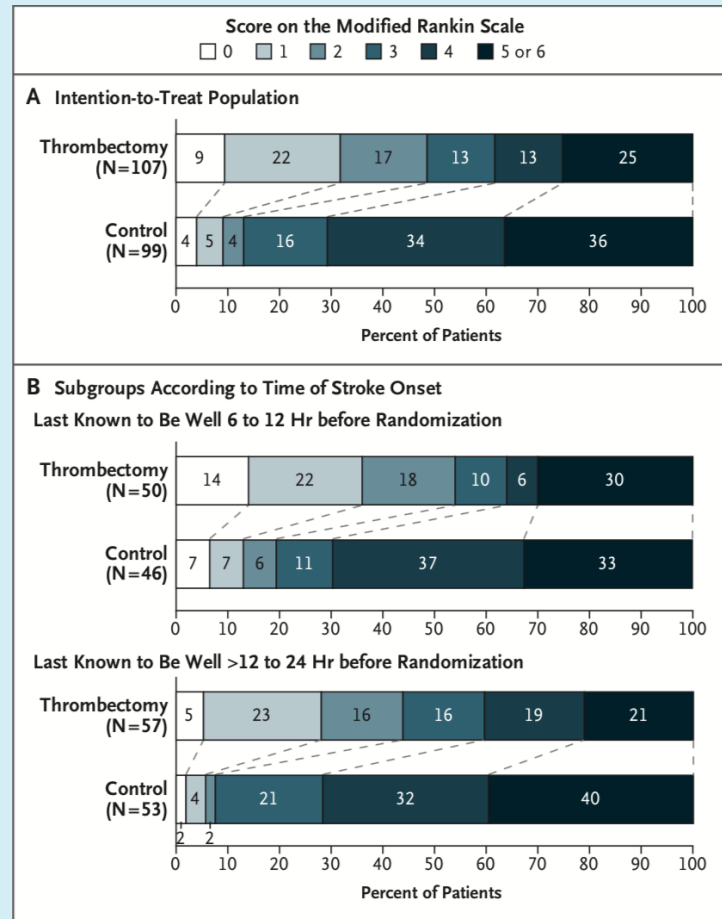
- Treatment 5.5 vs. Control 3.4
- Adjusted difference 2 points (95% 1.1-3.0)
- Posterior probability of superiority >0.999

2nd Primary Outcome (mRS 0,1 or 2):

- Treatment 49% vs. Control 13%
- Adjusted difference 33% (95% 21-44)
- Posterior probability of superiority >0.999

Post hoc sensitivity analysis accounting for baseline differences in groups: thrombectomy remained significant.

RESULTS - PRIMARY

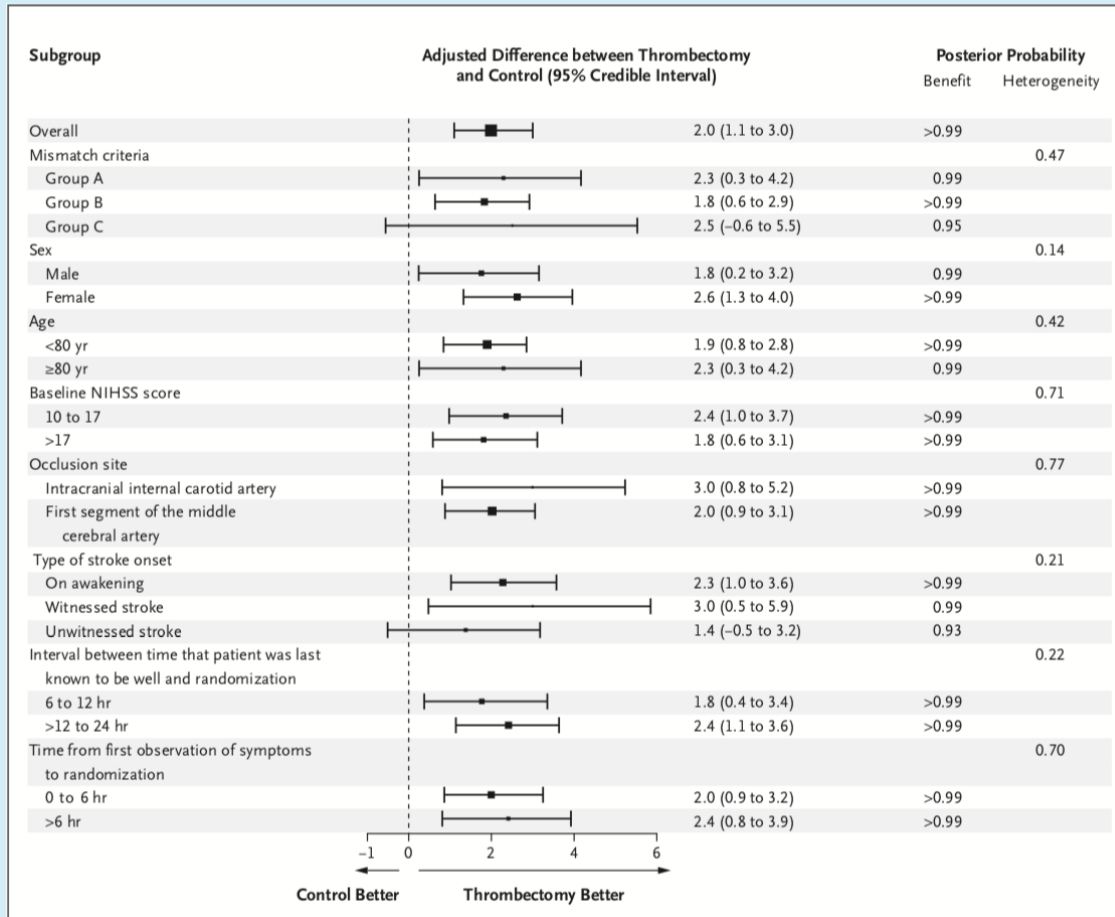


RESULTS

Table 2. Efficacy Outcomes.*

Outcome	Thrombectomy Group (N = 107)	Control Group (N = 99)	Absolute Difference (95% CI) [†]	Adjusted Difference (95% Credible Interval) [‡]	Posterior Probability of Superiority
Primary end points					
Score on utility-weighted modified Rankin scale at 90 days [§]	5.5±3.8	3.4±3.1	2.1 (1.2–3.1)	2.0 (1.1–3.0)	>0.999
Functional independence at 90 days — no. (%) [¶]	52 (49)	13 (13)	36 (24–47)	33 (21–44)	>0.999
				Risk Ratio (95% CI)	P Value
Secondary end points					
Early response — no. (%)	51 (48)	19 (19)	29 (16–41)	3 (2–4)	<0.001**
Recanalization at 24 hr — no. (%) ^{††}	82 (77)	39 (39)	40 (27–52)	2 (2–4)	<0.001**
Change from baseline in infarct volume at 24 hr — ml ^{†††}					0.003 ^{‡‡}
Median	1	13			
Interquartile range	0–28	0–42			
Infarct volume at 24 hour — ml ^{†††}					<0.001 ^{‡‡}
Median	8	22			
Interquartile range	0–48	8–68			
Grade of 2b or 3 on mTICI scale — no. (%) ^{§§}	90 (84)	NA			

RESULTS - SUBGROUP



SAFETY OUTCOMES

Table 3. Safety Outcomes.*

Outcome	Thrombectomy Group (N = 107)	Control Group (N = 99)	Absolute Difference (95% CI)	Risk Ratio (95% CI)
	<i>no. (%)</i>		<i>percentage points</i>	
Stroke-related death at 90 days	17 (16)	18 (18)	-2 (-13 to 8)	1 (1 to 2)
Death from any cause at 90 days	20 (19)	18 (18)	1 (-10 to 11)	1 (1 to 2)
Symptomatic intracranial hemorrhage at 24 hr†	6 (6)	3 (3)	3 (-3 to 8)	2 (1 to 7)
Neurologic deterioration at 24 hr‡	15 (14)	26 (26)	-12 (-23 to -1)	1 (0 to 1)
Procedure-related complications	7 (7)	NA		
Distal embolization in a different territory	4 (4)	NA		
Intramural arterial dissection	2 (2)	NA		
Arterial perforation	0	NA		
Access-site complications leading to intervention	1 (1)	NA		

DISCUSSION

In patients with a salvageable penumbra on perfusion scans, a 'late' thrombectomy results in better neurological outcomes than standard medical care alone.

Rates of functional independence (49%) were similar to groups in Goyal's Meta-analysis of thrombectomy at 6 hours (46%).

Provides further evidence for the 'tissue window' over the traditional 'time window'.

Outcomes seem consistent across the subgroups (except group C) but analysis limited by inadequate power.

DISCUSSION

Control group baseline characteristics slightly worse

Poor rate of functional independence in the control group (13%) compared to similar groups in other trials (26%).

Possible explanation:

- worse baseline prognostic factors (age, higher NIHSS scores)
- the nature of late presentation stroke (6-24 hours)
- potentially related to low use of tPA (13% vs. 88% in Goyal's)

Trend towards poorer outcomes amongst patients with larger infarct volumes (group C)

DISCUSSION

Paid for and supervised by the company that sells the retrieval device.

Trial was ceased early at 200 of a potential 500 patients.

Use of unconventional end-points (Utility-weighted modified Rankin Score)

DISCUSSION

Results not generalizable to ALL stroke patients, and certainly not all 'late' presenting stroke patients.

- Only patients with relatively small infarct areas and large penumbras – a small minority of stroke presentations.
- 'Wake up' stroke was 6-24 post last known to be well but only 5 hours post wake up.

Traditional 'time window' practices are likely still more important for the majority of patients.

- Early recognition and early reperfusion – time is still a good surrogate for tissue
- Best method of reperfusion still up for debate

DISCUSSION

Quick word on Basilar territory infarct:

Reperfusion traditionally strongly recommended given the often 'stuttering' symptom onset of vertigo, dysarthria that progresses to coma and dire natural progression of untreated stroke.

Good outcomes rare after 9 hours of coma.

Target within 6 hours but based on minimal evidence.

Kumar et al 2015: Meta-analysis of observational data showed clear benefit of recanalization.

Pending trials:

BASICS and BEST.

DEFUSE 3

Thrombectomy for Stroke at 6 to 16 hours with selection by Perfusion Imaging. Albers G. et. al. NEJM Feb 2018.

Multicenter, randomised, open label trial, with blinded outcome assessment. 38 US hospitals

6 to 16 hours since they were last known to be well

ICA and proximal MCA stroke with infarct size **<70ml**

Ischaemic penumbra to infarct ratio **>1.8**

Standard therapy PLUS thrombectomy vs. Standard medical therapy alone.

DEFUSE 3 RESULTS

Terminated early after 182 patients had been randomised

- 92 treatment vs. 90 to control

Improved functional independence (mRS 0-2)

- 45% vs. 17% in control

Improved 90 day mortality

- 14% vs. 26% in control

Favorable shift in distribution of functional outcome on mRS

FUTURE

Hope that perfusion scanning will help us direct therapy to those most likely to benefit from it.

- Patient /penumbra directed reperfusion therapy independent of time since stroke onset
- Limit exposure to systemic thrombolysis in those unlikely to benefit

Pending trials in this area:

WAKE-UP: Efficacy and safety of MRI based thrombolysis in wake-up stroke

EXTEND: Extending the time for thrombolysis in emergency neurological deficits

IMPLICATIONS FOR PRACTICE