HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Acute Stroke Treatments:
Rapid Review of the Latest Data

Scott Silverman, MD
MGH Stroke Service
September 21, 2018

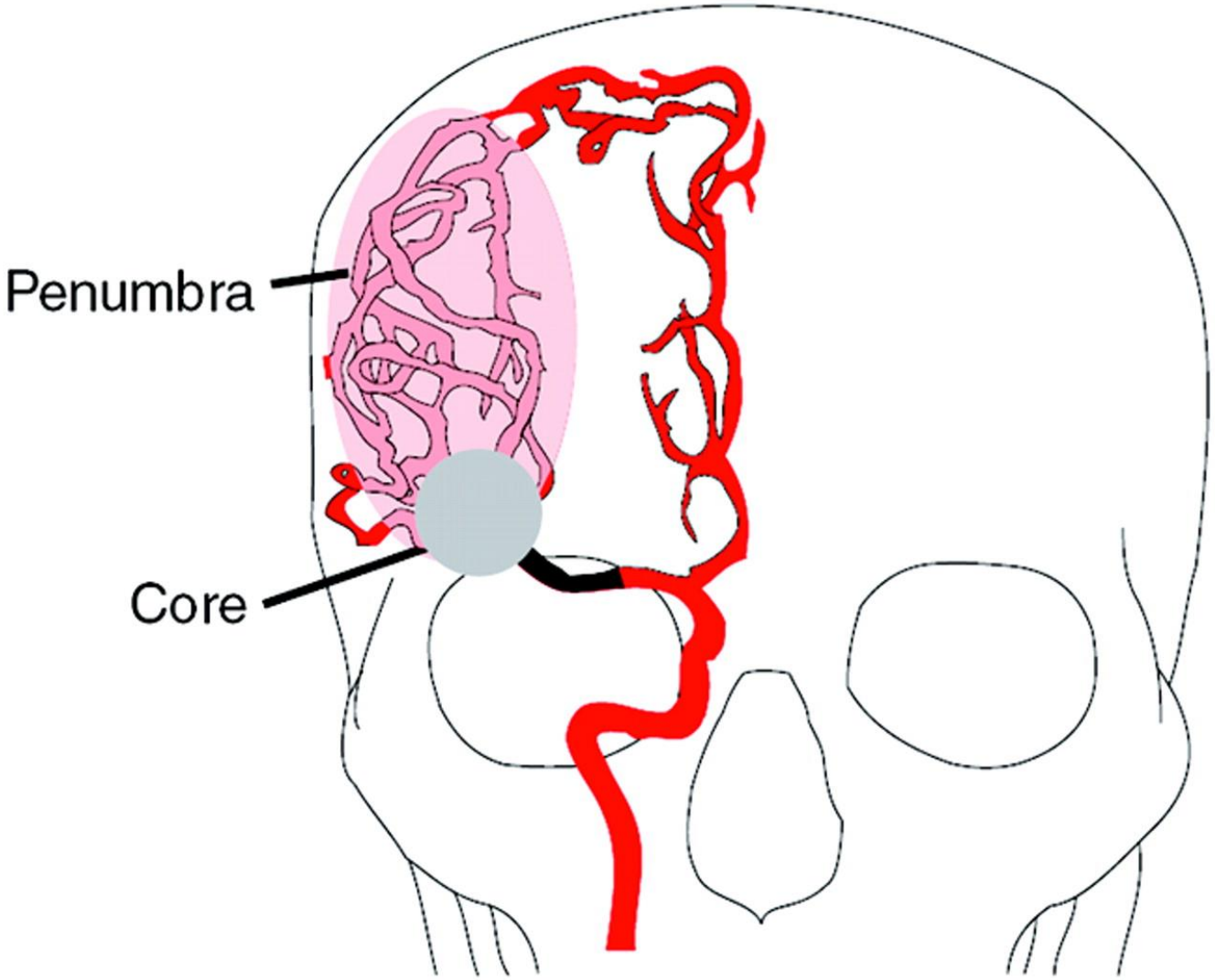
MASSACHUSETTS
GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Disclosure Statement of Financial Interest

I, Scott Silverman, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

All TCT 2018 faculty disclosures are listed online and on the App.

Core and Penumbra



MASSACHUSETTS
GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Gonzalez, AJNR, 2006

Importance of Large Vessel Occlusions (LVO)

- Larger infarcts, more severe deficits, worse outcomes
- > 33% of acute stroke
- > 60% dependence and death (mRS 3-6) after all stroke
- > 90% death post-stroke after all stroke

Malhotra et al, Frontiers Neurology, 2017

IAT: The Standard of Care in 2015


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 1, 2015 VOL. 372 NO. 1

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

O.A. Berkhemer, P.S.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J.H. Wermer, M.A.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L.M. de Kort, W.J.J. van Rooij, J.S.P. van den Berg, B.A.A.M. van Hasselt, L.A.M. Aerden, R.J. Dallinga, M.C. Visser, J.C.J. Bot, P.C. Vroomen, O. Eshghi, T.H.C.M.L. Schreuder, R.J.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E.S. Sprengers, S.F.M. Jenniskens, L.F.M. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B.W.E.M. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B.L.M. Majoie, and D.W.J. Dippel, for the MR CLEAN Investigators*

ABSTRACT

BACKGROUND

In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion, intraarterial treatment is highly effective for emergency revascularization. However, proof of a beneficial effect on functional outcome is lacking.

METHODS

We randomly assigned eligible patients to either intraarterial treatment plus usual care or usual care alone. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that was confirmed on vessel imaging and that could be treated intraarterially within 6 hours after symptom onset. The primary outcome was the modified Rankin scale score at 90 days; this categorical scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). The treatment effect was estimated with ordinal logistic regression as a common odds ratio, adjusted for prespecified prognostic factors. The adjusted common odds ratio measured the likelihood that intraarterial treatment would lead to lower (ie, more favorable) Rankin scores, as compared with usual care alone (shift analysis).

RESULTS

We enrolled 500 patients at 16 medical centers in the Netherlands (233 assigned to intraarterial treatment and 267 to usual care alone). The mean age was 65 years (range, 23 to 96), and 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intraarterial treatment. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (modified Rankin score, 0 to 2) in favor of the intervention (32.6% vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.

CONCLUSIONS

In patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe. (Funded by the Dutch Heart Foundation and others; MR CLEAN Netherlands Trial Registry number, NTR1804, and Current Controlled Trials number, ISRCTN10888758.)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

M. Goyal, A.M. Demchuk, B.K. Menon, M. Eesa, J.L. Rempel, J. Thornton, D. Roy, T.G. Jovin, R.A. Willinsky, B.L. Sapkota, D. Dowlatshahi, D.F. Frei, N.R. Kamal, W.J. Montanera, A.Y. Poppe, K.J. Ryckborst, F.L. Silver, A. Shuaib, D. Tampieri, D. Williams, O.Y. Bang, B.W. Baxter, P.A. Burns, H. Choe, J.-H. Heo, C.A. Holmstedt, B. Jankowski, M. Kelly, G. Linares, J.L. Mandzia, J. Shankar, S.-I. Sohn, R.H. Swartz, P.A. Barber, S.B. Coutts, E.E. Smith, W.F. Morrish, A. Weill, S. Subramaniam, A.P. Mitha, J.H. Wong, M.W. Lowerison, T.T. Sajobi, and M.D. Hill for the ESCAPE Trial Investigators*

ABSTRACT

BACKGROUND

Among patients with a proximal vessel occlusion in the anterior circulation, 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment. We evaluated rapid endovascular treatment in addition to standard care in patients with acute ischemic stroke with a small infarct core, a proximal intracranial arterial occlusion, and moderate-to-good collateral circulation.

METHODS

We randomly assigned participants to receive standard care (control group) or standard care plus endovascular treatment with the use of available thrombectomy devices (intervention group). Patients with a proximal intracranial occlusion in the anterior circulation were included up to 12 hours after symptom onset. Patients with a large infarct core or poor collateral circulation on computed tomography (CT) and CT angiography were excluded. Workflow times were measured against predetermined targets. The primary outcome was the score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) at 90 days. A proportional odds model was used to calculate the common odds ratio as a measure of the likelihood that the intervention would lead to lower scores on the modified Rankin scale than would control care (shift analysis).

RESULTS

The trial was stopped early because of efficacy. At 22 centers worldwide, 316 participants were enrolled, of whom 238 received intravenous alteplase (120 in the intervention group and 118 in the control group). In the intervention group, the median time from study CT of the head to first reperfusion was 84 minutes. The rate of functional independence (90-day modified Rankin score of 0 to 2) was increased with the intervention (53.0%, vs. 29.3% in the control group; P<0.001). The primary outcome favored the intervention (common odds ratio, 2.6; 95% confidence interval, 1.7 to 3.8; P<0.001), and the intervention was associated with reduced mortality (18.4%, vs. 19.0% in the control group; P=0.04). Symptomatic intracerebral hemorrhage occurred in 3.6% of participants in intervention group and 2.7% of participants in control group (P=0.75).

CONCLUSIONS

Among patients with acute ischemic stroke with a proximal vessel occlusion, a small infarct core, and moderate-to-good collateral circulation, rapid endovascular treatment improved functional outcomes and reduced mortality. (Funded by Covidien and others; ESCAPE ClinicalTrials.gov number, NCT01778335.)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

T.G. Jovin, A. Chamorro, E. Cobo, M.A. de Miquel, C.A. Molina, A. Rovira, L. San Román, J. Serena, S. Abilleira, M. Ribó, M. Millán, X. Urra, P. Cardona, E. López-Cancio, A. Tomasello, C. Castaño, J. Blasco, L. Aja, L. Dorado, H. Quesada, M. Rubiera, M. Hernández-Pérez, M. Goyal, A.M. Demchuk, R. von Kummer, M. Gallofré, and A. Dávalos, for the REVASCAT Trial Investigators*

ABSTRACT

BACKGROUND

We aimed to assess the safety and efficacy of thrombectomy for the treatment of stroke in a trial embedded within a population-based stroke reperfusion registry.

METHODS

During a 2-year period at four centers in Catalonia, Spain, we randomly assigned 206 patients who could be treated within 8 hours after the onset of symptoms of acute ischemic stroke to receive either medical therapy (including intravenous alteplase when eligible) and endovascular therapy with the Solitaire stent retriever (thrombectomy group) or medical therapy alone (control group). All patients had confirmed proximal anterior circulation occlusion and the absence of a large infarct on neuroimaging. In all study patients, the use of alteplase either did not achieve revascularization or was contraindicated. The primary outcome was the severity of global disability at 90 days, as measured on the modified Rankin scale (ranging from 0 [no symptoms] to 6 [death]). Although the maximum planned sample size was 690, enrollment was halted early because of loss of equipoise after positive results for thrombectomy were reported from other similar trials.

RESULTS

Thrombectomy reduced the severity of disability over the range of the modified Rankin scale (adjusted odds ratio for improvement of 1 point, 1.7; 95% confidence interval [CI], 1.09 to 2.8) and led to higher rates of functional independence (a score of 0 to 2) at 90 days (43.7% vs. 28.2%; adjusted odds ratio, 2.1; 95% CI, 1.1 to 4.0). At 90 days, the rates of symptomatic intracranial hemorrhage were 1.9% in both the thrombectomy group and the control group (P=1.00), and rates of death were 18.4% and 15.5%, respectively (P=0.68). Registry data indicated that only eight patients who met the eligibility criteria were treated outside the trial at participating hospitals.

CONCLUSIONS

Among patients with anterior circulation stroke who could be treated within 8 hours after symptom onset, stent retriever thrombectomy reduced the severity of poststroke disability and increased the rate of functional independence. (Funded by Fundació Ictus Malaltia Vascular through an unrestricted grant from Covidien and others; REVASCAT ClinicalTrials.gov number, NCT01076270.)


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2015 VOL. 372 NO. 24

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

Jeffrey L. Saver, M.D., Mayank Goyal, M.D., Alain Bonafe, M.D., Hans-Christoph Diener, M.D., Ph.D., Elad I. Levy, M.D., Vitor M. Pereira, M.D., Gregory W. Albers, M.D., Christophe Cognard, M.D., David J. Cohen, M.D., Werner Hacke, M.D., Ph.D., Olav Jansen, M.D., Ph.D., Tudor G. Jovin, M.D., Heinrich P. Mattle, M.D., Raul G. Nogueira, M.D., Adnan H. Siddiqui, M.D., Ph.D., Dileep R. Yavagal, M.D., Blaise W. Baxter, M.D., Thomas G. Devlin, M.D., Ph.D., Demetrius K. Lopes, M.D., Vivek K. Reddy, M.D., Richard du Mesnil de Rochemont, M.D., Oliver C. Singer, M.D., and Reza Jahan, M.D., for the SWIFT PRIME Investigators*

ABSTRACT

BACKGROUND

Among patients with acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, less than 40% regain functional independence when treated with intravenous tissue plasminogen activator (t-PA) alone. Thrombectomy with the use of a stent retriever, in addition to intravenous t-PA, increases reperfusion rates and may improve long-term functional outcome.

METHODS

We randomly assigned eligible patients with stroke who were receiving or had received intravenous t-PA to continue with t-PA alone (control group) or to undergo endovascular thrombectomy with the use of a stent retriever within 6 hours after symptom onset (intervention group). Patients had confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic-core lesions. The primary outcome was the severity of global disability at 90 days, as assessed by means of the modified Rankin scale (with scores ranging from 0 [no symptoms] to 6 [death]).

RESULTS

Thrombectomy reduced the severity of disability over the range of the modified Rankin scale (adjusted odds ratio for improvement of 1 point, 1.7; 95% confidence interval [CI], 1.09 to 2.8) and led to higher rates of functional independence (a score of 0 to 2) at 90 days (43.7% vs. 28.2%; adjusted odds ratio, 2.1; 95% CI, 1.1 to 4.0). At 90 days, the rates of symptomatic intracranial hemorrhage were 1.9% in both the thrombectomy group and the control group (P=1.00), and rates of death were 18.4% and 15.5%, respectively (P=0.68). Registry data indicated that only eight patients who met the eligibility criteria were treated outside the trial at participating hospitals.

CONCLUSIONS

Among patients with anterior circulation stroke who could be treated within 8 hours after symptom onset, stent retriever thrombectomy reduced the severity of poststroke disability and increased the rate of functional independence. (Funded by Fundació Ictus Malaltia Vascular through an unrestricted grant from Covidien and others; REVASCAT ClinicalTrials.gov number, NCT01076270.)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

B.C.V. Campbell, P.J. Mitchell, T.J. Kleinig, H.M. Dewey, L. Churilov, N. Yassi, B. Yan, R.J. Dowling, M.W. Parsons, T.J. Oxley, T.Y. Wu, M. Brooks, M.A. Simpson, F. Miteff, C.R. Levi, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, M. Priglinger, T. Ang, R. Scroop, P.A. Barber, B. McGuinness, T. Wijeratne, T.G. Phan, W. Chong, R.V. Chandra, C.F. Bladin, M. Badve, H. Rice, L. de Villiers, H. Ma, P.M. Desmond, G.A. Donnan, and S.M. Davis, for the EXTEND-IA Investigators*

ABSTRACT

BACKGROUND

Trials of endovascular therapy for ischemic stroke have produced variable results. We conducted this study to test whether more advanced imaging selection, recently developed devices, and earlier intervention improve outcomes.

METHODS

We randomly assigned patients with ischemic stroke who were receiving 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischemic stroke either to undergo endovascular thrombectomy with the Solitaire FR (Flow Restoration) stent retriever or to continue receiving alteplase alone. All the patients had occlusion of the internal carotid or middle cerebral artery and evidence of salvageable brain tissue and ischemic core of less than 70 ml on computed tomographic (CT) perfusion imaging. The coprimary outcomes were reperfusion at 24 hours and early neurologic improvement (≥8-point reduction on the National Institutes of Health Stroke Scale or a score of 0 or 1 at day 5). Secondary outcomes included the functional score on the modified Rankin scale at 90 days.

RESULTS

The trial was stopped early because of efficacy after 70 patients had undergone randomization (35 patients in each group). The percentage of ischemic territory that had undergone reperfusion at 24 hours was greater in the endovascular-therapy group than in the alteplase-only group (median, 100% vs. 37%; P<0.001). Endovascular therapy, initiated at a median of 210 minutes after the onset of stroke, increased early neurologic improvement at 5 days (89% vs. 37%, P=0.002) and improved the functional outcome at 90 days, with more patients achieving functional independence (score of 0 to 2 on the modified Rankin scale, 71% vs. 40%; P=0.01). There were no significant differences in rates of death or symptomatic intracerebral hemorrhage.

CONCLUSIONS

In patients with ischemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging, early thrombectomy with the Solitaire FR stent retriever, as compared with alteplase alone, improved reperfusion, early neurologic recovery, and functional outcome. (Funded by the Australian National Health and Medical Research Council and others; EXTEND-IA ClinicalTrials.gov number, NCT01492725, and Australian New Zealand Clinical Trials Registry number, ACTRN12612000960965.)

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

MASSACHUSETTS GENERAL HOSPITAL

FIREMAN VASCULAR CENTER

HERMES

- Meta-analysis of pooled individual patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA)
- 1287 subjects (634 endovascular & 653 standard medical)
- Acute ischemic stroke – LVO of anterior circulation
- 2nd generation thrombectomy devices
- Randomized to endovascular therapy plus standard care versus standard care
- Primary Outcome: disability on mRS at 90 days

Goyal et al, Lancet, 2016

HERMES: Results

	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
mRS score reduction (shift analysis; primary outcome)*	..	..	..	..	2·26* (1·67–3·06); p<0·0001	..	2·49* (1·76–3·53); p<0·0001
mRS score 0–1 at 90 days	26·9% (170/633)	12·9% (83/645)	14·0	2·00 (1·54–2·60); p<0·0001	2·49 (1·84–3·35); p<0·0001	2·06 (1·59–2·69); p<0·0001	2·72 (1·99–3·71); p<0·0001
mRS score 0–2 at 90 days	46·0% (291/633)	26·5% (171/645)	19·5	1·7 (1·41–2·05); p<0·0001	2·35 (1·85–2·98); p<0·0001	1·73 (1·43–2·09); p<0·0001	2·71 (2·07–3·55); p<0·0001
NIHSS score 0–2 at 24 h	21·0% (129/615)	8·3% (52/630)	12·7	2·47 (1·79–3·41); p<0·0001	2·91 (2·06–4·12); p<0·0001	2·66 (1·92–3·67); p<0·0001	3·77 (2·49–5·71); p<0·0001
Early neurological recovery at 24 h	50·2% (309/616)	21·2% (134/633)	29·0	2·34 (1·91–2·87); p<0·0001	4·04 (2·75–5·93); p<0·0001	2·34 (1·91–2·87); p<0·0001	4·36 (3·03–6·27); p<0·0001

NNT = 2.6

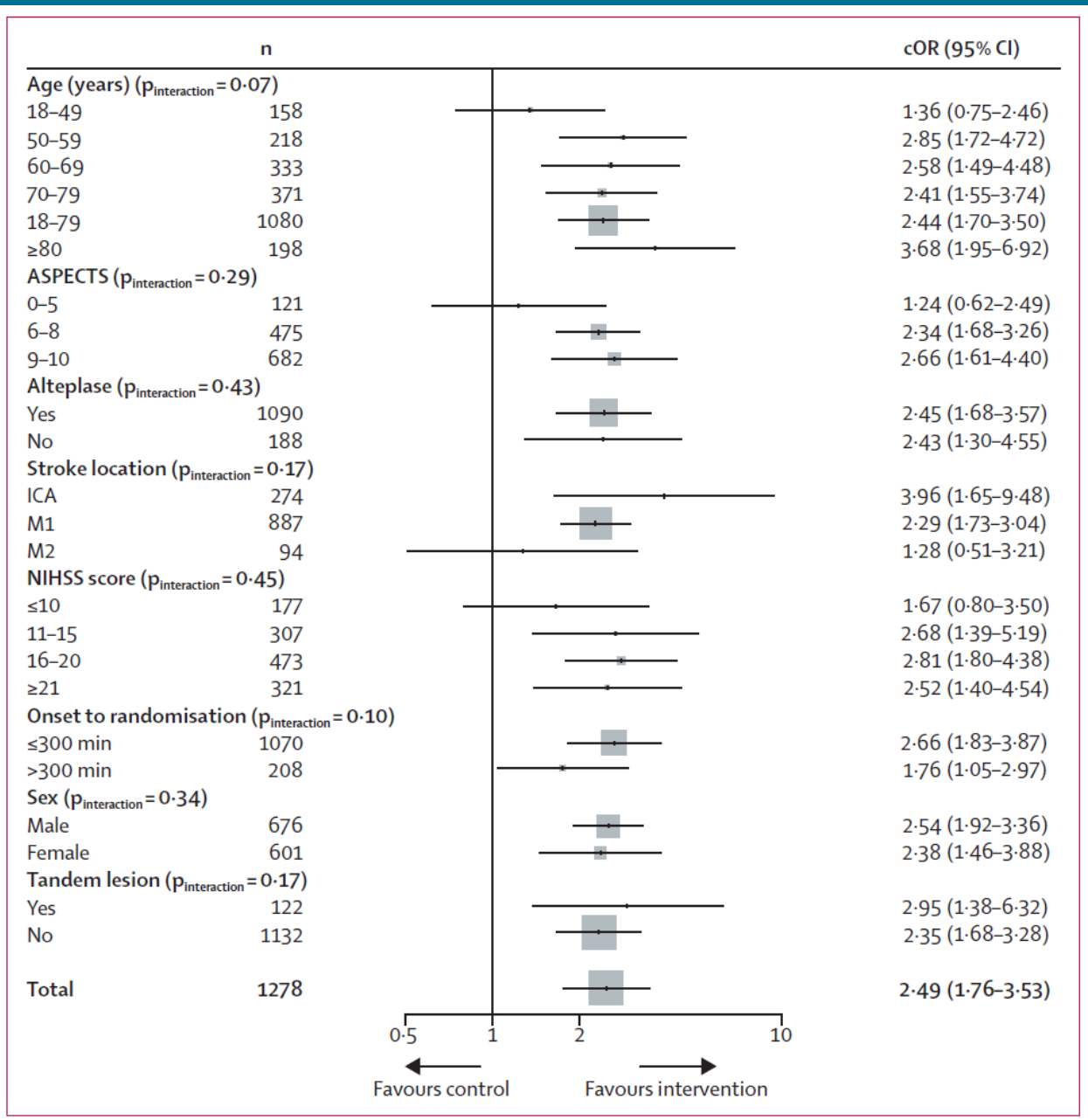
Data show the proportion of patients with outcome (n/N), unless otherwise stated. NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. *Common odds ratio indicating the odds of improvement of 1 point on the mRS.

Table 2: Efficacy outcomes from the pooled data

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Goyal et al, Lancet 2016

HERMES: Subgroup Analysis



Goyal et al, Lancet 2016

CHUSETTS
AL HOSPITAL
AN VASCULAR CENTER

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

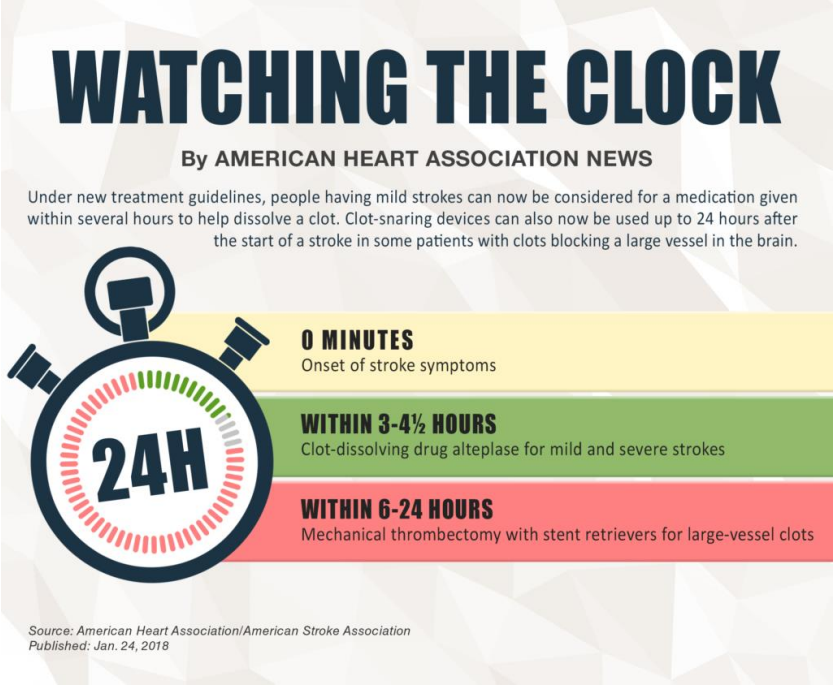
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
3. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.	I	A	Recommendation revised from 2015 Endovascular.

Powers et al, Stroke, 2018

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

IAT: Extended Time Window



MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 4, 2018 VOL. 378 NO. 1

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*

DAWN™ TRIAL

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

FIREMAN VASCULAR CENTER

Nogueira et al, NEJM, 2018

Dawn Trial

- Multicenter (26), RCT, 206 pts
- Thrombectomy: Trevo (Stryker) – retrievable stent
- Occlusion of intracranial ICA, prox MCA (M1) or both
- LSW 6-24 hours
- NIHSS ≥ 10, mRS 0-1
- Mismatch: clinical to core infarct volume
  - Age ≥80, infarct ≤ 20 cc
  - Age <80, NIHSS 10-19, infarct ≤ 30 cc
  - Age <80, NIHSS ≥ 20, infarct > 30 cc to ≤ 50 cc

Nogueira et al, NEJM, 2018

Dawn Trial 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

NNT = 2

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Nogueira et al, NEJM, 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

G.W. Albers, M.P. Marks, S. Kemp, S. Christensen, J.P. Tsai, S. Ortega-Gutierrez, R.A. McTaggart, M.T. Torbey, M. Kim-Tenser, T. Leslie-Mazwi, A. Sarraj, S.E. Kasner, S.A. Ansari, S.D. Yeatts, S. Hamilton, M. Mlynash, J.J. Heit, G. Zaharchuk, S. Kim, J. Carrozzella, Y.Y. Palesch, A.M. Demchuk, R. Bammer, P.W. Lavori, J.P. Broderick, and M.G. Lansberg, for the DEFUSE 3 Investigators*

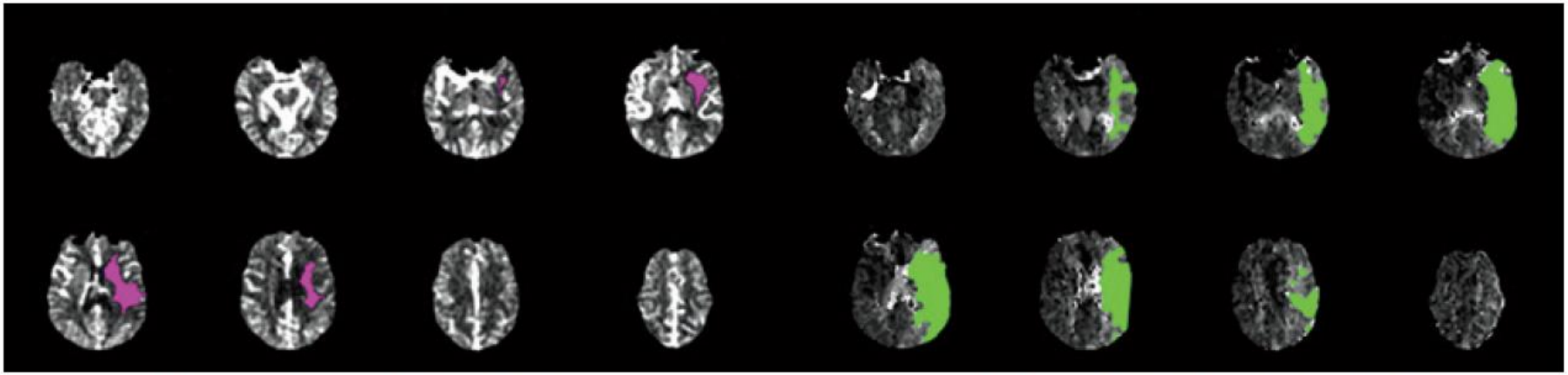
defuse·3

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

DEFUSE 3 Trial

- Multicenter (38), RCT, NIH-funded, 182 pts
- Occlusion of cervical or intracranial ICA, or prox MCA (M1)
- Thrombectomy: any FDA-approved device
- LSW 6-16 hours
- Imaging mismatch:
  - Core ≤ 70 cc, mismatch ratio (Penumbra/Core) ≥1.8, and mismatch volume ≥15 cc (RAPID software, iSchemaview)

DEFUSE 3



Volume of Ischemic Core, 23 ml

Volume of Perfusion Lesion, 128 ml

Mismatch volume, 105 ml
Mismatch ratio, 5.6

Figure 1. Example of Perfusion Imaging Showing a Disproportionately Large Region of Hypoperfusion as Compared with the Size of Early Infarction.

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Albers et al, NEJM, 2018

DEFUSE 3 Results

Table 2. Clinical and Imaging Outcomes.

Outcome	Endovascular Therapy (N=92)*	Medical Therapy (N=90)	Odds Ratio or Risk Ratio (95% CI)†	P Value
Primary efficacy outcome: median score on modified Rankin scale at 90 days (IQR)‡	3 (1–4)	4 (3–6)	2.77 (1.63–4.70)§	<0.001
Secondary efficacy outcome: functional independence at 90 days — no. (%)¶	41 (45)	15 (17)	2.67 (1.60–4.48)	<0.001
Safety outcomes — no. (%)				
Death at 90 days	13 (14)	23 (26)	0.55 (0.30–1.02)	0.05
Symptomatic intracranial hemorrhage‖	6 (7)	4 (4)	1.47 (0.40–6.55)	0.75
Early neurologic deterioration	8 (9)	11 (12)	0.71 (0.30–1.69)	0.44
Parenchymal hematoma type 2	8 (9)	3 (3)	2.61 (0.73–14.69)	0.21

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Albers et al, NEJM, 2018

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
7. In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.	I	A	New recommendation.
8. In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	IIa	B-R	New recommendation.

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Powers et al, Stroke, 2018

Device: ADAPT vs Stentriever

JAMA | Original Investigation

Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion

The ASTER Randomized Clinical Trial

Bertrand Lapergue, MD, PhD; Raphael Blanc, MD, MSc; Benjamin Gory, MD, PhD; Julien Labreuche, BST; Alain Duhamel, PhD; Gautier Marnat, MD; Suzana Saleme, MD; Vincent Costalat, MD, PhD; Serge Bracard, MD; Hubert Desal, MD, PhD; Mikael Mazighi, MD, PhD; Arturo Consoli, MD; Michel Piotin, MD, PhD; for the ASTER Trial Investigators

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Lapergue et al, JAMA, 2018

ASTER Trial

- Multicenter (8), RCT, France, 381 pts
- Occlusion of intracranial ICA, or MCA (M1 or M2)
- Thrombectomy: ADAPT vs stent-retriever (Trevo or Solitaire)
- LSW <6 hours
- Primary outcome: mTICI 2b or 3

Lapergue et al, JAMA, 2018

ASTER

Table 2. Primary and Secondary Efficacy Outcomes

Outcomes	No./Total (%)[a] First-Line Contact Aspiration (n = 192)	First-Line Stent Retriever (n = 189)	Risk Difference, % (95% CI)[b]	Odds Ratio (95% CI)	*P* Value
Primary Efficacy Outcome					
Successful revascularization at the end of all procedures					
mTICI score of 2b or 3 assessed by core laboratory[c,d]					
Intention-to-treat analysis[e]	164/192 (85.4)	157/189 (83.1)	2.4 (−5.4 to 9.7)	1.20 (0.68-2.10)	.53
Per-protocol analysis	140/153 (91.5)	140/165 (84.9)	6.8 (−0.6 to 14.11)	1.91 (0.93-3.91)	.08
mTICI score of 2b or 3 assessed at study site[d,f]	163/192 (84.9)	163/189 (86.2)	−1.4 (−8.3 to 5.5)	0.90 (0.50-1.59)	.71
Clinical Efficacy Outcomes					
Change in NIHSS score at 24 h, mean (95% CI)[g]	−4.8 (−6.1 to −3.6)[h]	−5.2 (−6.5 to −3.9)[h]	0.38 (−1.42 to 2.18)[i]	NA	.68
Functional independence at 3 mo[j]	82/181 (45.3)	91/182 (50.0)	−4.6 (−14.7 to 6.1)	0.83 (0.54-1.26)	.38
Modified Rankin Scale score at 3 mo, median (interquartile range)	3.0 (1.0 to 5.0)	2.5 (1.0 to 5.0)	NA	0.76 (0.53-1.10)[k]	.15

ADAPT ~ Stentriever

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Lapergue et al, JAMA, 2018

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
12. The use of mechanical thrombectomy devices other than stent retrievers as first-line devices for mechanical thrombectomy may be reasonable in some circumstances, but stent retrievers remain the first choice.	IIb	B-R	Recommendation revised from 2015 Endovascular.

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Powers et al, Stroke, 2018

Anesthesia: GA vs Conscious Sedation

JAMA Neurology | Original Investigation

Effect of General Anesthesia and Conscious Sedation During Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic Stroke
A Randomized Clinical Trial

Claus Z. Simonsen, MD, PhD; Albert J. Yoo, MD, PhD; Leif H. Sørensen, MD; Niels Juul, MD; Søren P. Johnsen, MD, PhD; Grethe Andersen, MD, DMSc; Mads Rasmussen, MD, PhD

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Simonsen et al, JAMA Neurology, 2018

GOLIATH Trial

- Single-center, prospective, RCT
- 128 pts with anterior circ occlusion, LSW < 6hrs
- Randomized to GA vs CS before IAT
- Primary outcome: infarct growth on 48-72 hr MRI

Simonsen et al, JAMA Neurology, 2018

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

GOLIATH Trial Results

Table 2. Primary and Secondary Imaging and Clinical Outcomes

Outcome	General Anesthesia (n = 65)	Conscious Sedation (n = 63)	*P* Value
Successful reperfusion (mTICI 2b-3), No. (%)	50 (76.9)	38 (60.3)	.04
Acute infarct volume, median (IQR), mL	10.5 (2.4-23.6)	13.3 (5.2-31.1)	.26
Final infarct volume, median (IQR), mL	22.3 (8.1-64.5)	38.0 (16.7-128.0)	.04
Infarct volume growth, median (IQR), mL	8.2 (2.2-38.6)	19.4 (2.4-79.0)	.10
90-d mRS score, median (IQR)	2 (1-3)	2 (1-4)	.04
NIHSS score in 24 h, median (IQR)	6 (3-14)	10 (2-19)	.19
Change in NIHSS score after 24 h, median (IQR)	−10 (−14 to −5)	−7 (−13 to 0)	.11

GA ~ CS

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Simonsen et al, JAMA Neurology, 2018

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

16. It is reasonable to select an anesthetic technique during endovascular therapy for AIS on the basis of individualized assessment of patient risk factors, technical performance of the procedure, and other clinical characteristics. Further randomized trial data are needed.	**IIa**	**B-R**	Recommendation revised from 2015 Endovascular.
Conscious sedation (CS) was widely used in the recent endovascular trials (90.9% of ESCAPE, 63% of SWIFT PRIME) with no clear positive or negative impact on outcome. In MR CLEAN, post hoc analysis showed a 51% (95% CI, 31–86) decrease in treatment effect of general anesthesia (GA) compared with CS.[180] In THRACE, 51 of 67 patients receiving GA and 43 of 69 patients receiving CS achieved TICI 2b/3 (P=0.059) with no impact on outcome.[106] Thirty-five of 67 patients with GA and 36 of 74 with CS had mRS scores of 0 to 2 at 90 days. Although several retrospective studies suggest that GA produces worsening of functional outcomes, there are limited prospective randomized data. Two small (≤150 participants) single-center RCTs have compared GA with CS. Both failed to show superiority of either treatment for the primary clinical end point.[181,182] Until further data are available, either method of procedural sedation is reasonable.			See Tables XLII and XLIII in online Data Supplement 1.

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Powers et al, Stroke, 2018

IV tPA for Unknown LSW

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 16, 2018 VOL. 379 NO. 7

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas, J. Fiehler, I. Ford, I. Galinovic, S. Gellissen, A. Golsari, J. Gregori, M. Günther, J. Guibernau, K.G. Häusler, M. Hennerici, A. Kemmling, J. Marstrand, B. Modrau, L. Neeb, N. Perez de la Ossa, J. Puig, P. Ringleb, P. Roy, E. Scheel, W. Schonewille, J. Serena, S. Sunaert, K. Villringer, A. Wouters, V. Thijs, M. Ebinger, M. Endres, J.B. Fiebach, R. Lemmens, K.W. Muir, N. Nighoghossian, S. Pedraza, and C. Gerloff, for the WAKE-UP Investigators*

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

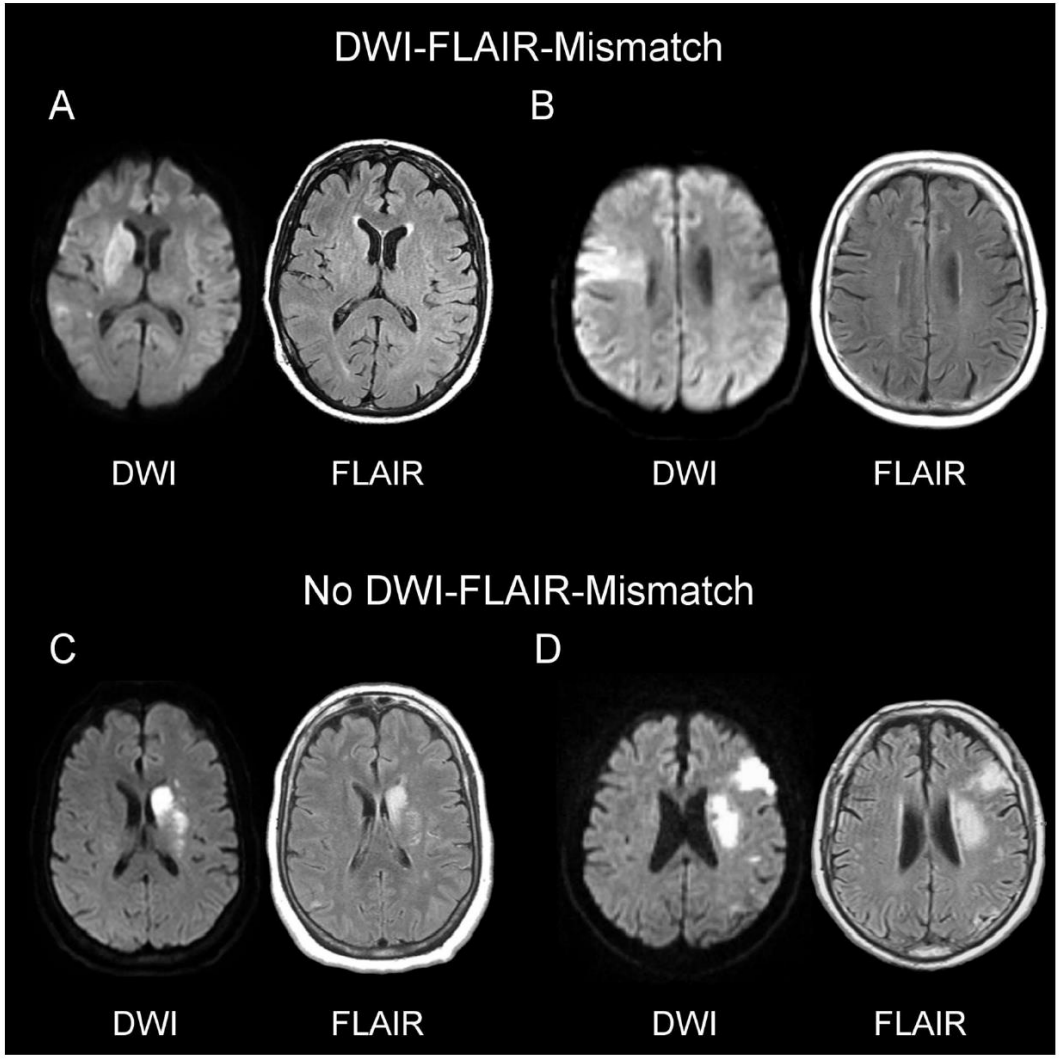
FIREMAN VASCULAR CENTER

Thomalla et al, NEJM, 2018

WAKE-UP Trial

- Multi-center, RCT, unknown time of onset
- Mismatch: DWI hyperintensity present and normal FLAIR
- Exclusion: IAT planned, >1/3 MCA territory, NIHSS > 25
- Randomization: 1:1 to IV tPA vs Placebo
- Stopped early due to funding
- Primary Outcome: mRS 0-1 at 90 days

WAKE-UP Trial



ACHUSETTS
RAL HOSPITAL
FIREMAN VASCULAR CENTER

Supp Index to WAKE-UP, NEJM, 2018

WAKE-UP Results

Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Alteplase Group (N = 254)	Placebo Group (N = 249)	Effect Variable	Adjusted Value (95% CI)†	P Value
Primary efficacy end point					
Favorable outcome at 90 days — no./total no. (%)‡	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02
Secondary efficacy end points					
Median score on modified Rankin scale at 90 days (IQR)§	1 (1–3)	2 (1–3)	Common odds ratio	1.62 (1.17 to 2.23)	0.003¶

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Thomalla et al, NEJM, 2018

IV Lytic: TNK vs tPA

EXTEND - IA TNK

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 26, 2018 VOL. 378 NO. 17

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey, V. Thijs, R. Scroop, M. Simpson, M. Brooks, H. Asadi, T.Y. Wu, D.G. Shah, T. Wijeratne, T. Ang, F. Miteff, C.R. Levi, E. Rodrigues, H. Zhao, P. Salvaris, C. Garcia-Esperon, P. Bailey, H. Rice, L. de Villiers, H. Brown, K. Redmond, D. Leggett, J.N. Fink, W. Collecutt, A.A. Wong, C. Muller, A. Coulthard, K. Mitchell, J. Clouston, K. Mahady, D. Field, H. Ma, T.G. Phan, W. Chong, R.V. Chandra, L.-A. Slater, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, C.F. Bladin, G. Sharma, P.M. Desmond, M.W. Parsons, G.A. Donnan, and S.M. Davis, for the EXTEND-IA TNK Investigators*

FIREMAN VASCULAR CENTER

Campbell et al, NEJM, 2018

EXTEND – IA TNK

EXTEND - IA TNK

- Multicenter, RCT, ischemic stroke, LSW < 4.5 hrs
- LVO: ICA, MCA (M1/M2), BA
- Randomization: IV tenectaplase (0.25 mg/kg) vs IV alteplase
- TNK: greater fibrin specificity and longer half-life
- Primary outcome: Angiographic = absence of thrombus or >50% reperfusion of target vessel

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Campbell et al, NEJM, 2018

EXTEND-IA TNK Results

Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Safety outcomes				
Death — no. (%)§	10 (10)	18 (18)		
Adjusted risk ratio			0.5 (0.3–1.0)	0.049
Adjusted odds ratio			0.4 (0.2–1.1)	0.08
Symptomatic intracerebral hemorrhage — no. (%)§‖	1 (1)	1 (1)		
Risk ratio			1.0 (0.1–15.9)	0.99
Odds ratio			1.0 (0.1–16.2)	0.99
Parenchymal hematoma — no. (%)§**	6 (6)	5 (5)		
Risk ratio			1.2 (0.4–3.8)	0.76
Odds ratio			1.2 (0.4–4.1)	0.76

Campbell et al, NEJM, 2018

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

IV tPA for Nondisabling Strokes?

JAMA | Original Investigation

Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits

The PRISMS Randomized Clinical Trial

Pooja Khatri, MD, MSc; Dawn O. Kleindorfer, MD; Thomas Devlin, MD; Robert N. Sawyer Jr, MD; Matthew Starr, MD; Jennifer Mejilla, DO; Joseph Broderick, MD; Anjan Chatterjee, MD; Edward C. Jauch, MD, MS; Steven R. Levine, MD; Jose G. Romano, MD; Jeffrey L. Saver, MD; Achala Vagal, MD, MS; Barbara Purdon, PhD; Jenny Devenport, PhD; Andrey Pavlov, PhD; Sharon D. Yeatts, PhD; for the PRISMS Investigators

Khatri et al, JAMA, 2018

PRISMS Trial

- Multi-center (75), double-blind, RCT, 313 pts
- Minor non-disabling stroke (NIHSS 0-5), LSW < 3 hrs
- Randomization: IV tPA vs ASA 325 mg
- Primary outcome: mRS 0-1 at 90 days
- Study terminated early by study sponsor due to low

Table 3. 90-Day Efficacy Results

Outcomes	No. (%)		Effect Estimate, Risk Difference or OR (95% CI)[a]
	Intravenous Alteplase + Oral Placebo (n = 156)	Intravenous Placebo + Oral Aspirin (n = 157)	
Primary Outcome			
mRS score of 0 or 1, adjusted[b]			−1.1 (−9.4 to 7.3)

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Khatri et al, JAMA, 2018

Mild, Disabling Stroke

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

For patients with mild but disabling stroke symptoms, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. There should be no exclusion for patients with mild but nonetheless disabling stroke symptoms, in the opinion of the treating physician, from treatment with IV alteplase because there is proven clinical benefit for those patients.† (*Class I; LOE B-R*)‡

Powers et al, Stroke, 2018

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

Summary of Pivotal 2018 Trial Results

- DAWN/DEFUSE 3: Extended time window for IAT
- ASTER: ADAPT = Stentriever
- GOLIATH: No change infarct growth with GA vs cons sed
- WAKE-UP: IV tPA using MRI in stroke unknown LSW
- EXTEND-IA TNK: TNK > Alteplase
- PRISMS: No benefit IV tPA in minor non-disabling stroke

Future Studies

- Thrombolytic: EXTEND-IA TNK 2
- Neuroprotectant: ESCAPE-NA1
- Device: COMPASS
- Large Core: TENSION, DEFUSE M
- Low NIHSS: ENDO LOW
- IAT vs IVT plus IAT: MR CLEAN-NO IV, SWIFT DIRECT
- Systems of Care: RACECAT

Special thanks to Dr. Ronil Chandra for assistance with the content of some of the above slides

MASSACHUSETTS GENERAL HOSPITAL
FIREMAN VASCULAR CENTER

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Thank you!

Scott Silverman, MD

MASSACHUSETTS
GENERAL HOSPITAL

FIREMAN VASCULAR CENTER