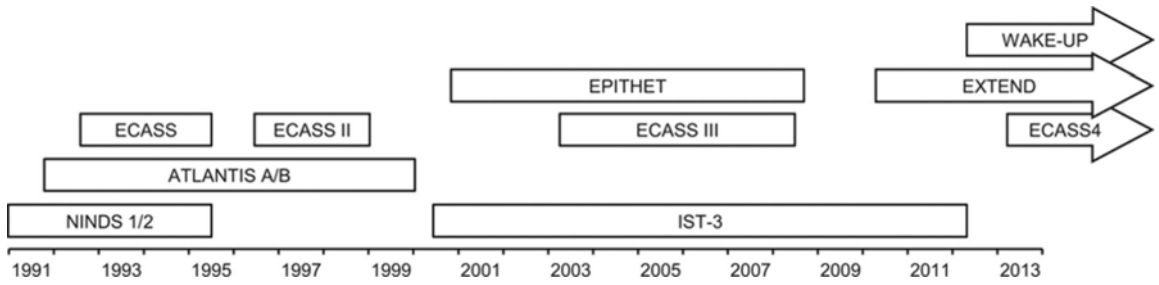
Late Window Thrombolysis

12th Annual Practical Management of Stroke Conference
October 2nd, 2020

G. Abbas Kharal MD. MPH
Staff, Cerebrovascular Division
Cleveland Clinic Neurological Institute

Evolution of IV Thrombolysis in Stroke

- NINDS IV TPA trial in 1995 showed significant benefit in functional outcomes with alteplase
- Pooled analysis of three randomized controlled trials (European Cooperative Acute Stroke Study ECASS I, ECASS II, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS]) showed potential benefit up to 4.5 hours
- ECASS III in 2008, randomized 821 patients to alteplase vs placebo within 4.5 hours, showed favorable outcomes in alteplase group (52.4% vs. 45.2%)
- Further meta-analysis data of pooled trials in 2014 showed benefit of tpa up to 4.5 hours
- AHA/ASA and European Stroke Guidelines extended tpa window to 4.5 hours



Evolution of Thrombolysis in Stroke

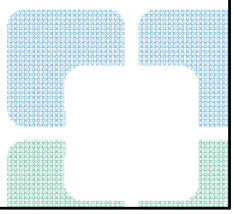
- Campbell, Bruce CV, et al. "Twenty-year history of the evolution of stroke thrombolysis with intravenous alteplase to reduce long-term disability." *Stroke* 46.8 (2015): 2341-2346.

Extending Thrombolysis Windows

Time based window vs Tissue Based Windows

Tissue Window vs Time Windows

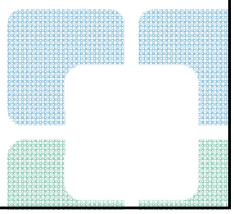
- 14% - 27% ischemic stroke patients wake up with stroke symptoms
- Unclear time of symptom onset
- Initial stroke event within a few hours of awakening.
- In such patients, the LKW time may not be an accurate marker of symptom onset
- Use of a tissue-window rather than time-window is needed

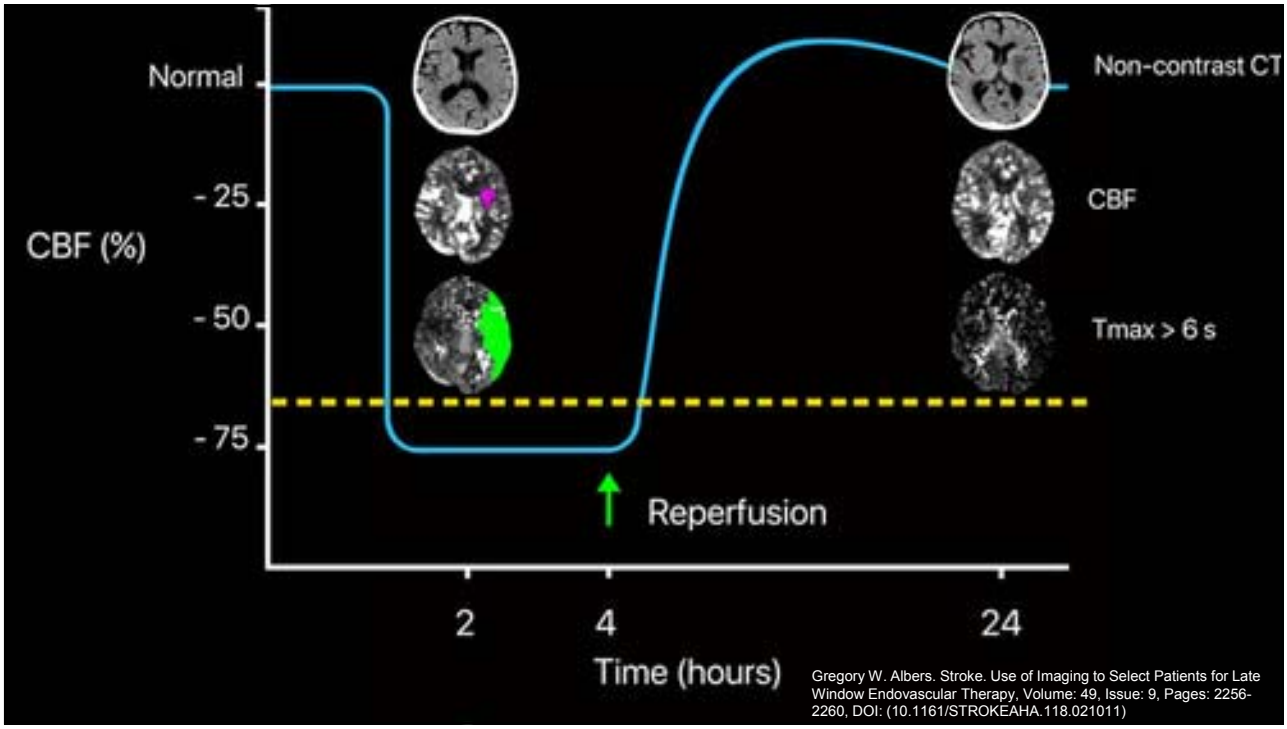


Advanced Imaging in Establishing Tissue Windows

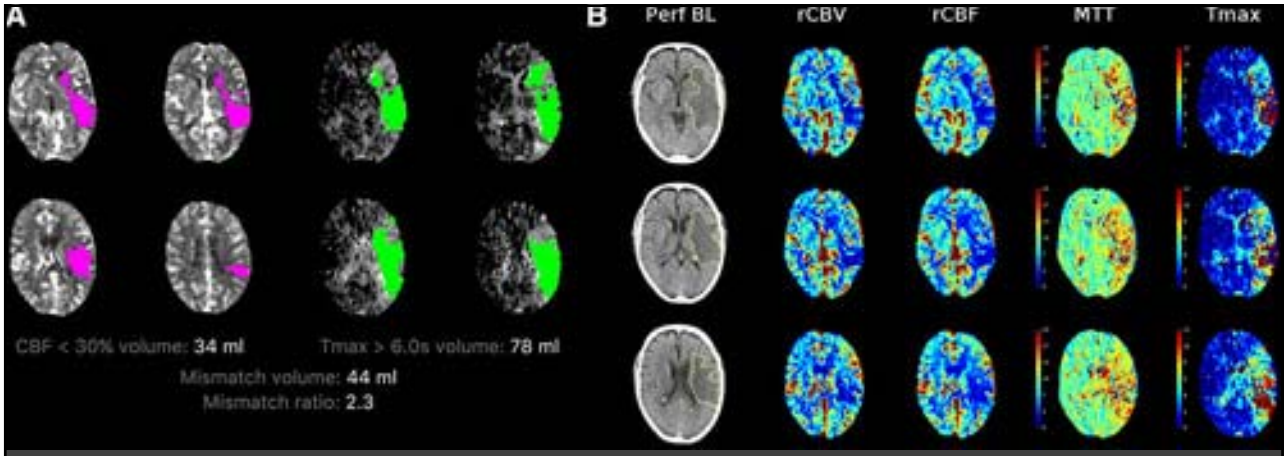
CTP & MRI Brain using advanced imaging software can

- Help better predict the time of onset of ischemic event
- Calculate infarct core
- Estimate potentially salvageable brain tissue



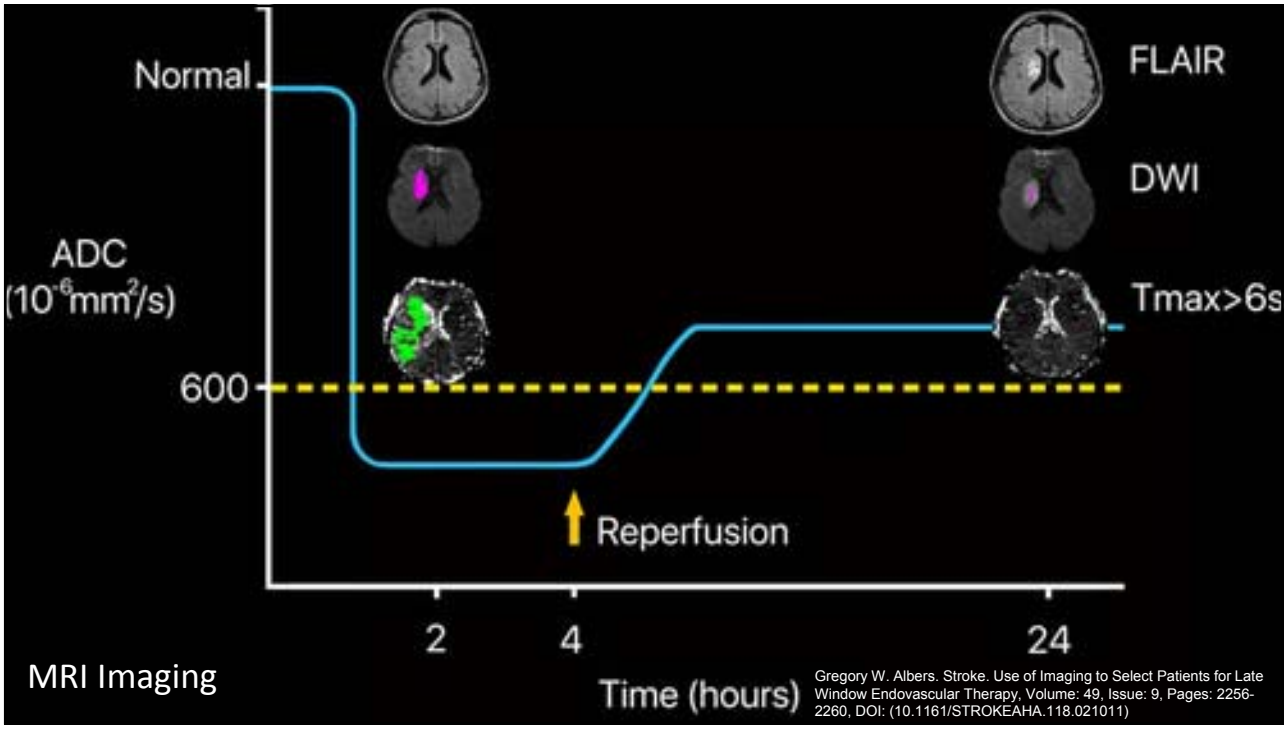


Gregory W. Albers. Stroke. Use of Imaging to Select Patients for Late Window Endovascular Therapy, Volume: 49, Issue: 9, Pages: 2256-2260, DOI: (10.1161/STROKEAHA.118.021011)



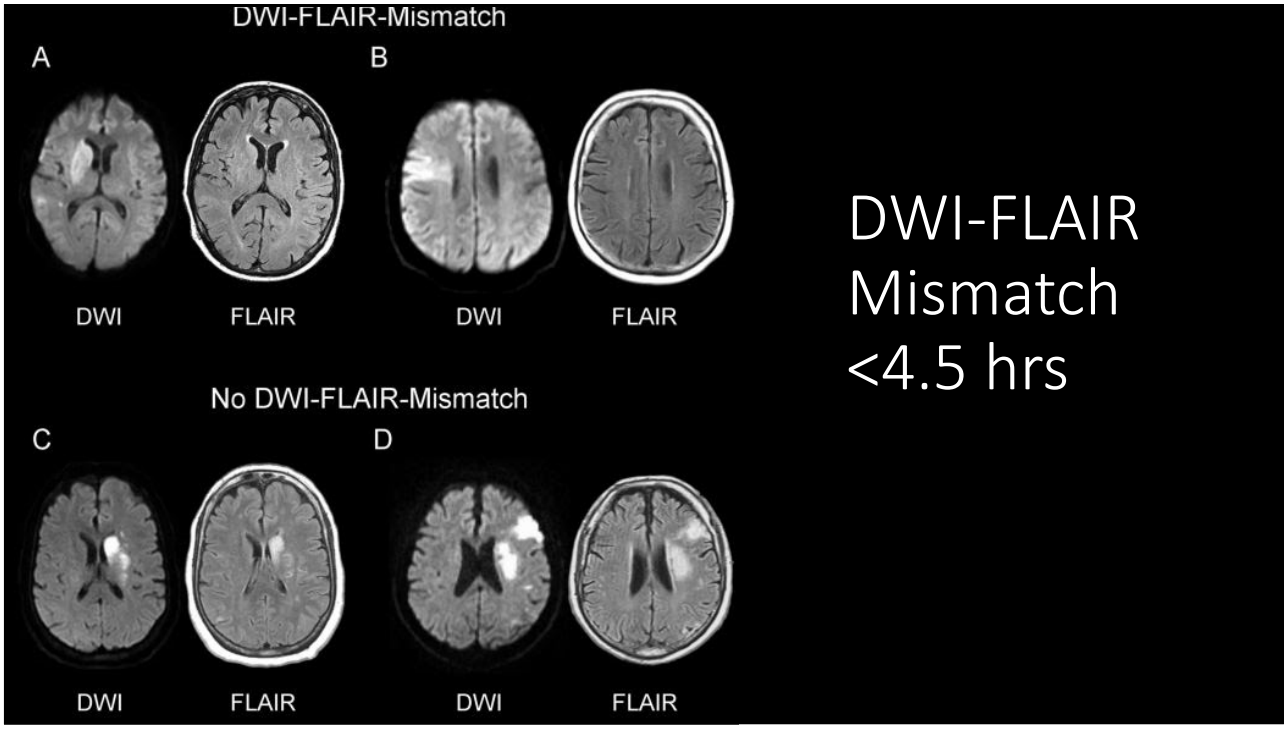
CT Perfusion Maps

Gregory W. Albers. Stroke. Use of Imaging to Select Patients for Late Window Endovascular Therapy, Volume: 49, Issue: 9, Pages: 2256-2260, DOI: (10.1161/STROKEAHA.118.021011)



MRI Imaging

Gregory W. Albers. Stroke. Use of Imaging to Select Patients for Late Window Endovascular Therapy, Volume: 49, Issue: 9, Pages: 2256-2260, DOI: (10.1161/STROKEAHA.118.021011)



DWI-FLAIR Mismatch <4.5 hrs

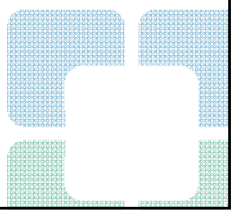
Advanced Imaging Parameters

CTP

- Infarct Core: rCBF <30%
- Penumbra: T.max > 6.0 seconds

MRI

- Infarct Core: ADC threshold of $<620\times10^{-3}$ mm/s
- FLAIR negative: <4.5 hours
- Penumbra: T.max > 6.0 seconds



Intravenous Thrombolysis in Unwitnessed Stroke Onset: MR WITNESS Trial Results

Lee H. Schwamm, MD,[1*] Ona Wu, PhD,[2*] Shlee S. Song, MD,[3] Lawrence L. Latour, PhD,[4] Andria L. Ford, MD,[5] Amie W. Hsia, MD,[4,6] Alona Muzikansky, MA,[7] Rebecca A. Betensky, PhD,[7,8] Albert J. Yoo, MD,[9,10] Michael H. Lev, MD,[10] Gregoire Boulouis, MD,[1,11] Arne Lauer, MD,[1] Pedro Cougo, MD,[1] William A. Copen, MD,[10] Gordon J. Harris, PhD,[10] and Steven Warach, MD, PhD,[12] on behalf of the MR WITNESS Investigators

Objective: Most acute ischemic stroke (AIS) patients with unwitnessed symptom onset are ineligible for intravenous thrombolysis due to timing alone. Lesion evolution on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) correlates with stroke duration, and quantitative mismatch of diffusion-weighted MRI with FLAIR (qDFM) might indicate stroke duration within guideline-recommended thrombolysis. We tested whether intravenous thrombolysis ≤4.5 hours from the time of symptom discovery is safe in patients with qDFM in an open-label, phase 2a, prospective study (NCT01282242).

Methods: Patients aged 18 to 85 years with AIS of unwitnessed onset at 4.5 to 24 hours since they were last known to be well, treatable within 4.5 hours of symptom discovery with intravenous alteplase (0.9mg/kg), and presenting with qDFM were screened across 14 hospitals. The primary outcome was the risk of symptomatic intracranial hemorrhage (sICH) with preplanned stopping rules. Secondary outcomes included symptomatic brain edema risk, and functional outcomes of 90-day modified Rankin Scale (mRS).

Results: Eighty subjects were enrolled between January 31, 2011 and October 4, 2015 and treated with alteplase at median 11.2 hours (IQR = 9.5–13.3) from when they were last known to be well. There was 1 sICH (1.3%) and 3 cases of symptomatic edema (3.8%). At 90 days, 39% of subjects achieved mRS = 0–1, as did 48% of subjects who had vessel imaging and were without large vessel occlusions.

Interpretation: Intravenous thrombolysis within 4.5 hours of symptom discovery in patients with unwitnessed stroke selected by qDFM, who are beyond the recommended time windows, is safe. A randomized trial testing efficacy using qDFM appears feasible and is warranted in patients without large vessel occlusions.

ANN NEUROL 2018;00:000–000

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

Key Points

- Randomly assigned patients with unknown “time of onset of stroke”, with ischemic lesion on DWI but no parenchymal hyperintensity on FLAIR, to iv alteplase vs placebo
- Primary Outcome Measure: Favorable outcome (mRS 0-1) at 90 days
- Secondary Outcome Measure: Likelihood that alteplase would lead to lower ordinal scores on the mRS than would placebo (shift analysis).
- 503 patients enrolled (Planned 800, stopped early 2/2 lack of funding)
- Statistically significant improvement in functional outcomes in iv alteplase arm but also higher rates of parenchymal hemorrhage (PH2)

Results

- A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (Adjusted OR 1.61; 95% confidence interval [CI], 1.09 to 2.36; P=0.02).
- The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (Adjusted Common OR 1.62; 95% CI, 1.17 to 2.23; P=0.003).
- There were 10 deaths (4.1%) in the alteplase group and 3 (1.2%) in the placebo group (OR 3.38; 95% CI, 0.92 to 12.52; P=0.07).
- The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (OR 4.95; 95% CI, 0.57 to 42.87; P=0.15).

WAKE Up Trial

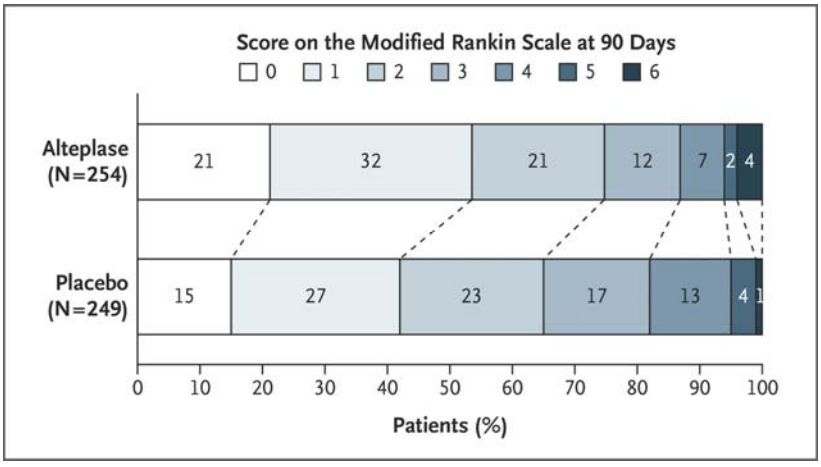


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Variable	Alteplase Group (N = 254)	Placebo Group (N = 249)
Mean age ±SD — yr	65.3±11.2	65.2±11.9
Male sex — no. (%)	165 (65.0)	160 (64.3)
Reason for unknown time of symptom onset — no. (%)		
Nighttime sleep	227 (89.4)	222 (89.2)
Daytime sleep	12 (4.7)	11 (4.4)
Aphasia, confusion, or other	15 (5.9)	16 (6.4)
Median interval between last time the patient was known to be well and symptom recognition (IQR) — hr	7.2 (4.7–8.7)	7.0 (5.0–9.0)
Medical history — no. (%)		
Arterial hypertension	135 (53.1)	131 (52.6)
Diabetes mellitus	43 (16.9)	39 (15.7)
Hypercholesterolemia	93 (36.6)	85 (34.1)
Atrial fibrillation	30 (11.8)	29 (11.6)
History of ischemic stroke	37 (14.6)	31 (12.4)
Median NIHSS score (IQR)†	6 (4–9)	6 (4–9)
Vessel occlusion on time-of-flight MRA — no./total no. (%)		
Any	84/249 (33.7)	84/246 (34.1)
Intracranial internal carotid artery	24/249 (9.6)	11/246 (4.5)
Middle cerebral artery main stem	35/249 (14.1)	37/246 (15.0)
Middle cerebral artery branch	32/249 (12.9)	36/246 (14.6)
Other‡	12/249 (4.8)	12/246 (4.9)
Median lesion volume on diffusion-weighted imaging (IQR) — ml	2.0 (0.8–7.9)	2.5 (0.7–8.8)
Median time from symptom recognition to MRI (IQR) — hr	2.6 (1.9–3.3)	2.6 (2.1–3.3)
Median time between end of MRI and treatment initiation (IQR) — min	25 (16–35)	26 (18–37)
Median time from symptom recognition to treatment initiation (IQR) — hr	3.1 (2.5–3.8)	3.2 (2.6–3.9)
Interval between last time that the patient was last known to be well and treatment initiation (IQR) — hr	10.3 (8.1–12.0)	10.4 (8.1–12.1)

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 to 3)	2 (1 to 3)	Common odds ratio	1.62 (1.17 to 2.23)	0.003¶
Correlation between treatment response at 90 days and deficit level at baseline — no./total no. (%)‖	72/246 (29.3)	44/244 (18.0)	Odds ratio	1.88 (1.22 to 2.89)	0.004¶
Global Outcome Score at 90 days**			Odds ratio	1.47 (1.07 to 2.04)	0.02¶
Median score on Beck Depression Inventory at 90 days (IQR)††	6.0 (2.0 to 11.0)	7.0 (2.0 to 14.0)	Mean difference ($\log_e$)	−0.04 (−0.22 to 0.15)	0.69¶
Total score on EQ-5D at 90 days‡‡	1.9±2.1	2.4±2.4	Mean difference	−0.52 (−0.88 to −0.16)	0.004¶
Score on visual analog scale on EQ-5D at 90 days§§	72.6±19.7	64.9±23.8	Mean difference	7.64 (3.75 to 11.51)	<0.001¶
Median infarct volume at 22–36 hr (IQR) — ml ¶¶	3.0 (0.8 to 17.7)	3.3 (1.1 to 16.6)	Mean difference ($\log_e$)	−0.16 (−0.47 to 0.15)	0.32¶

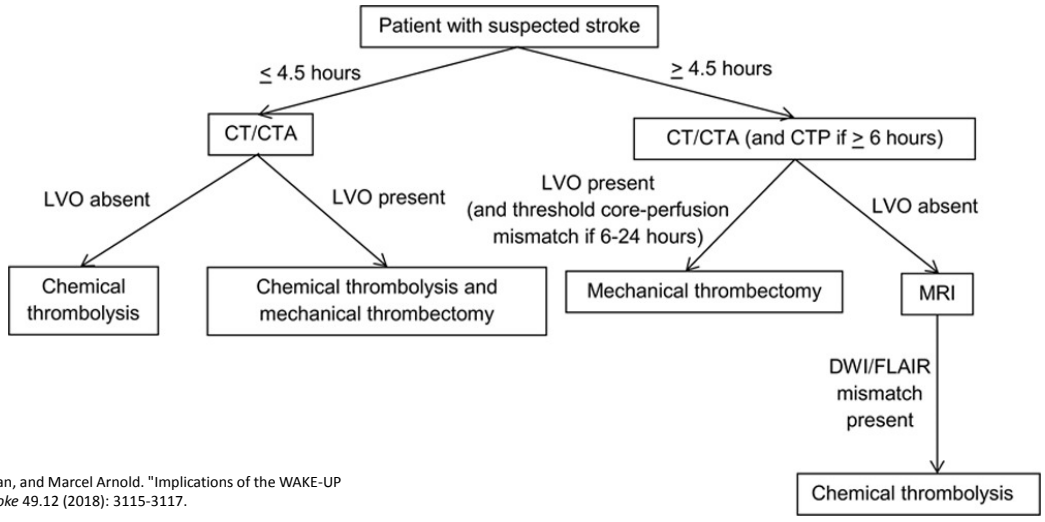
Table 3. Safety Outcomes.

Outcome	Alteplase Group (N=251)	Placebo Group (N=244)	Adjusted Odds Ratio (95% CI)*	P Value
	no. (%)			
Primary†				
Death or dependency at 90 days	33 (13.5)	44 (18.3)	0.68 (0.39–1.18)	0.17
Death at 90 days	10 (4.1)	3 (1.2)	3.38 (0.92–12.52)	0.07
Secondary				
Symptomatic intracranial hemorrhage				
As defined in SITS-MOST‡	5 (2.0)	1 (0.4)	4.95 (0.57–42.87)	0.15
As defined in ECASS II§	7 (2.8)	3 (1.2)	2.40 (0.60–9.53)	0.21
As defined in ECASS III¶	6 (2.4)	1 (0.4)	6.04 (0.72–50.87)	0.10
As defined in NINDS‖	20 (8.0)	12 (4.9)	1.78 (0.84–3.71)	0.13
Parenchymal hemorrhage type 2**	10 (4.0)	1 (0.4)	10.46 (1.32–82.77)	0.03
Other††				
Space-occupying brain infarction or edema with clinical deterioration	6 (2.4)	2 (0.8)		
Recurrent ischemic stroke				
Asymptomatic‡‡	58 (23.1)	55 (22.5)		
Symptomatic	17 (6.8)	8 (3.3)		
Major extracranial bleeding	3 (1.2)	0		
Severe anaphylactic reaction	0	1 (0.4)		

Conclusion:

- In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days.

Proposed Algorithm of Extended Window IVT



Silver, Brian, and Marcel Arnold. "Implications of the WAKE-UP Trial." *Stroke* 49.12 (2018): 3115-3117.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 9, 2019 VOL. 380 NO. 19

Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

H. Ma, B.C.V. Campbell, M.W. Parsons, L. Churilov, C.R. Levi, C. Hsu, T.J. Kleinig, T. Wijeratne, S. Curtze, H.M. Dewey, F. Miteff, C.-H. Tsai, J.-T. Lee, T.G. Phan, N. Mahant, M.-C. Sun, M. Krause, J. Sturm, R. Grimley, C.-H. Chen, C.-J. Hu, A.A. Wong, D. Field, Y. Sun, P.A. Barber, A. Sabet, J. Jannes, J.-S. Jeng, B. Clissold, R. Markus, C.-H. Lin, L.-M. Lien, C.F. Bladin, S. Christensen, N. Yassi, G. Sharma, A. Bivard, P.M. Desmond, B. Yan, P.J. Mitchell, V. Thijs, L. Carey, A. Meretoja, S.M. Davis, and G.A. Donnan, for the EXTEND Investigators*

Key Points

- Multicenter, randomized, placebo-controlled trial of patients with ischemic stroke who had hypoperfused but salvageable regions of brain detected on automated perfusion imaging
- Randomly assigned to receive intravenous alteplase or placebo between 4.5 and 9.0 hours after the onset of stroke or on awakening with stroke (if within 9 hours from the midpoint of sleep).
- The primary outcome was a score of 0 or 1 on the modified Rankin scale, on which scores range from 0 (no symptoms) to 6 (death), at 90 days.
- After 225 of the planned 310 patients had been enrolled, the trial was terminated because of a loss of equipoise after the publication of positive results from WAKE-UP trial
- A total of 113 patients were randomly assigned to the alteplase group and 112 to the placebo group.

Patient Selection

- Of the 225 patients enrolled, 65% of the patients had stroke symptoms upon awakening.
- CTP or perfusion-diffusion MRI images were used to assess infarct core and perfusion deficit using Rapid Processing of Perfusion and Diffusion (RAPID) automated software (iSchemaView, Menlo Park, CA).
- Perfusion lesion to infarct core mismatch was defined as a ratio greater than 1.2 between the volume of hypoperfused but salvageable tissue and the volume of the infarct core
- Absolute difference in volume greater than 10 ml
- Infarct core volume of less than 70 ml.

Results

- The primary outcome occurred in 40 patients (35.4%) in the alteplase group and in 33 patients (29.5%) in the placebo group (adjusted risk ratio, 1.44; 95% confidence interval [CI], 1.01 to 2.06; P=0.04).
- Symptomatic intracerebral hemorrhage occurred in 7 patients (6.2%) in the alteplase group and in 1 patient (0.9%) in the placebo group (adjusted risk ratio, 7.22; 95% CI, 0.97 to 53.5; P=0.05).

Table 1. Characteristics of the Patients at Baseline.*

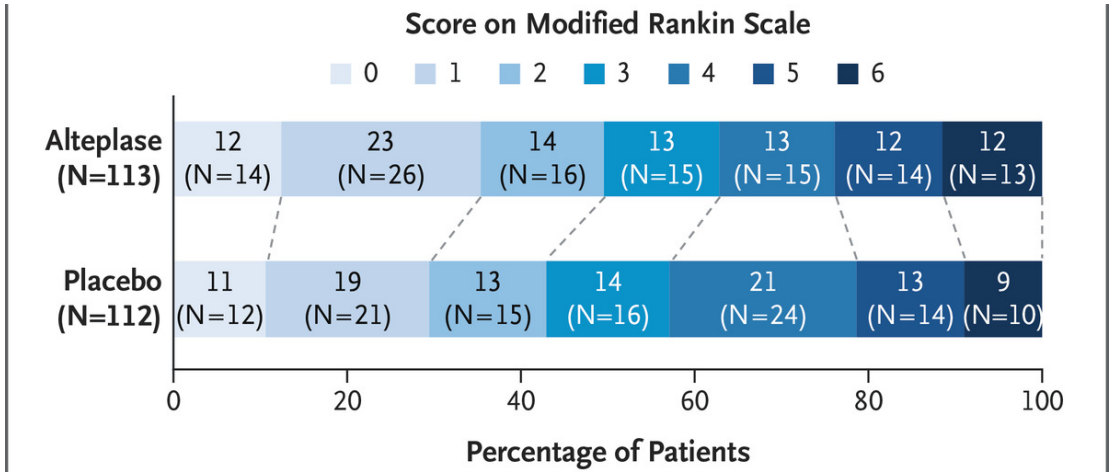
Characteristic	Alteplase (N=113)	Placebo (N=112)
Age — yr	73.7±11.7	71.0±12.7
Male sex — no. (%)	59 (52.2)	66 (58.9)
Median NIHSS score (IQR)†	12.0 (8.0–17.0)	10.0 (6.0–16.5)
Clinical history of atrial fibrillation — no. (%)	46 (40.7)	36 (32.1)
Geographic region — no. (%)		
Australia, New Zealand, and Finland	90 (79.6)	88 (78.6)
Taiwan	23 (20.4)	24 (21.4)
Time from stroke onset to randomization — no. (%)		
>4.5 to 6.0 hr	12 (10.6)	11 (9.8)
>6.0 to 9.0 hr	28 (24.8)	28 (25.0)
Awoke with stroke symptoms‡	73 (64.6)	73 (65.2)
Median time from stroke onset to hospital arrival (IQR) — min	308 (227–362)	293 (230–357)
Median time from stroke onset to initiation of intravenous therapy (IQR) — min	432 (374–488)	450 (374–500)
Median time from hospital arrival to initiation of intravenous therapy (IQR) — min	124 (81–179)	127 (87–171)
Imaging result		
Large-vessel occlusion — no.(%)§	78 (69.0)	81 (72.3)
Median volume of irreversibly injured ischemic-core tissue at initial imaging (IQR) — ml¶	4.6 (0–23.2)	2.4 (0–19.5)
Median perfusion-lesion volume at initial imaging (IQR) — ml‖	74.3 (40.1–134.0)	78 (47.7–111.8)

H Ma et al. N Engl J Med 2019;380:1795-1803.

Table 2. Efficacy and Safety Outcomes.*

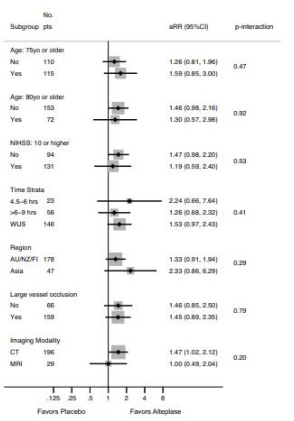
Outcome	Alteplase (N=113)	Placebo (N=112)	Adjusted Effect Size (95% CI)†	P Value	Unadjusted Effect Size (95% CI)†	P Value
	no./total no. (%)					
Primary outcome						
Score of 0 to 1 on the modified Rankin scale at 90 days‡	40/113 (35.4)	33/112 (29.5)	1.44 (1.01–2.06)	0.04	1.2 (0.82–1.76)	0.35
Secondary outcomes						
Score on the modified Rankin scale at 90 days						
0	14/113 (12.4)	12/112 (10.7)				
1	26/113 (23.0)	21/112 (18.8)				
2	16/113 (14.2)	15/112 (13.4)				
3	15/113 (13.3)	16/112 (14.3)				
4	15/113 (13.3)	24/112 (21.4)				
5	14/113 (12.4)	14/112 (12.5)				
6	13/113 (11.5)	10/112 (8.9)				
Functional improvement§			1.55 (0.96–2.49)		1.18 (0.74–1.87)	
Functional independence¶	56/113 (49.6)	48/112 (42.9)	1.36 (1.06–1.76)		1.16 (0.87–1.54)	
Percentage of reperfusion at 24 hr						
≥90%	53/106 (50.0)	31/109 (28.4)	1.73 (1.22–2.46)		1.76 (1.23–2.51)	
≥50%	76/106 (71.7)	57/109 (52.3)	1.35 (1.09–1.67)		1.37 (1.10–1.70)	
Tertiary outcomes						
Recanalization at 24 hr	72/107 (67.3)	43/109 (39.4%)	1.68 (1.29–2.19)		1.71 (1.30–2.23)	
Major neurologic improvement‖						
At 24 hr	27/113 (23.9)	11/112 (9.8)	2.76 (1.45–5.26)		2.43 (1.27–4.67)	
At 72 hr	32/112 (28.6)	22/112 (19.6)	1.56 (0.97–2.52)		1.45 (0.90–2.34)	
At 90 days	59/101 (58.4)	49/99 (49.5)	1.17 (0.91–1.52)		1.18 (0.91–1.53)	
Safety outcomes						
Death within 90 days after intervention	13/113 (11.5)	10/112 (8.9)	1.17 (0.57–2.40)	0.67	1.29 (0.59–2.82)	0.53
Symptomatic intracranial hemorrhage within 36 hr after intervention	7/113 (6.2)	1/112 (0.9)	7.22 (0.97–53.54)	0.053	6.94 (0.86–55.73)	0.07

Primary Outcome



H Ma et al. N Engl J Med 2019;380:1795-1803.

Figure S4. Pre-specified subgroup analyses for the primary outcome (modified Rankin scale 0-1)



H Ma et al. N Engl J Med 2019;380:1795-1803

Conclusion:

- Among the patients in this trial who had ischemic stroke and salvageable brain tissue, the use of alteplase between 4.5 and 9.0 hours after stroke onset or at the time the patient awoke with stroke symptoms resulted in a higher percentage of patients with no or minor neurologic deficits than the use of placebo.
- There were more cases of symptomatic cerebral hemorrhage in the alteplase group than in the placebo group.

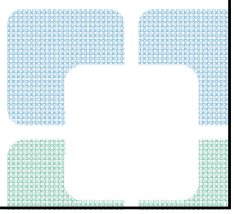
Meta-Analysis Data for Extending Thrombolysis

- Meta-analysis of EXTEND, ECASS4-EXTEND, and EPITHET published in 2019
- Of the 414 patients included in the three trials, 213 (51%) were assigned to receive alteplase and 201 (49%) were assigned to receive placebo.
- Overall, 211 patients in the alteplase group and 199 patients in the placebo group had mRS assessment data at 3 months and thus were included in the analysis of the primary outcome.
- 76 (36%) of 211 patients in the alteplase group and 58 (29%) of 199 patients in the placebo group had achieved excellent functional outcome at 3 months (adjusted odds ratio [OR] 1·86, 95% CI 1·15–2·99, p=0·011).
- Symptomatic intracerebral haemorrhage was more common in the alteplase group than the placebo group (ten [5%] of 213 patients *vs* one [<1%] of 201 patients in the placebo group; adjusted OR 9·7, 95% CI 1·23–76·55, p=0·031).

Campbell, Bruce CV, et al. "Extending thrombolysis to 4· 5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data." *The Lancet* 394.10193 (2019): 139-147.

Future Directions

- Can IVT be extended beyond 9 hours?
- Better thrombolytic agents?
- Real world implications



The NEW ENGLAND JOURNAL of MEDICINE

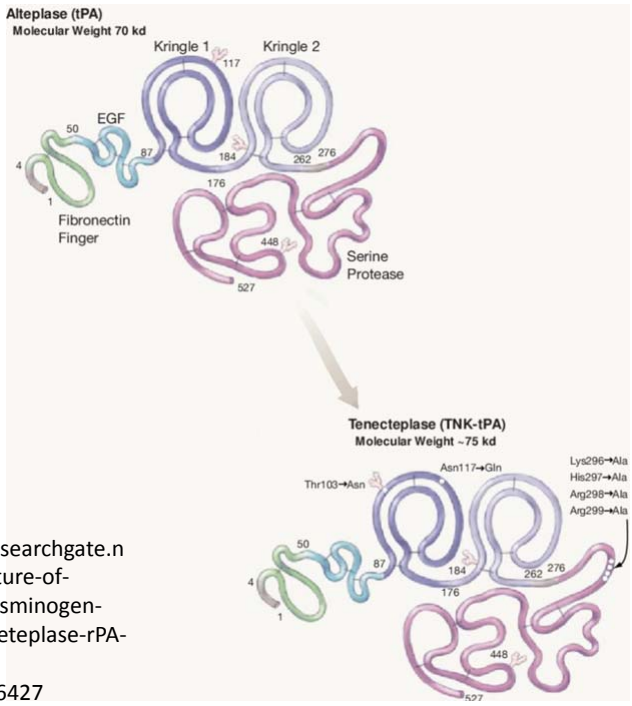
ESTABLISHED IN 1812 APRIL 26, 2018 VOL. 378 NO. 17

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

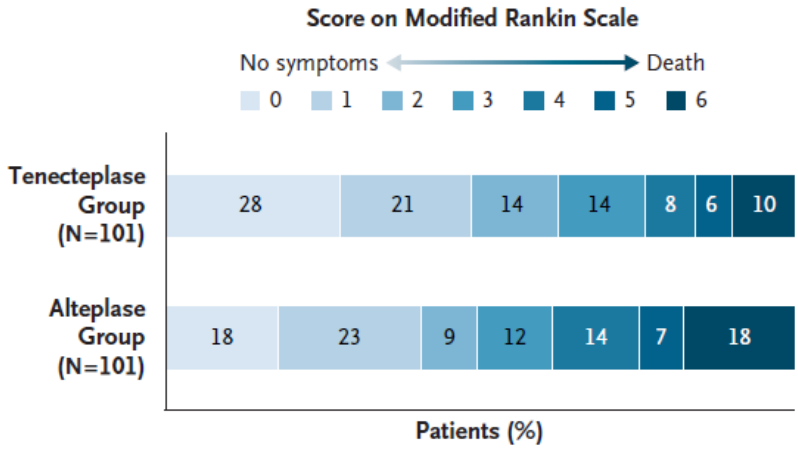
B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey, V. Thijs, R. Scroop, M. Simpson, M. Brooks, H. Asadi, T.Y. Wu, D.G. Shah, T. Wijeratne, T. Ang, F. Miteff, C.R. Levi, E. Rodrigues, H. Zhao, P. Salvaris, C. Garcia-Esperon, P. Bailey, H. 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*

Background: Tenecteplase

- 3-point mutated, bioengineered, 75 kDa variant of alteplase
  - Longer half-life
  - Higher fibrin specificity
  - Increased resistance to plasminogen activator inhibitor-1
  - Approved by FDA for treatment of MI in 2000
  - Cost: $5,800



https://www.researchgate.net/figure/Structure-of-Tissue-Type-Plasminogen-Activator-tPA-Reteplase-rPA-Lanoteplase-nPA_fig2_11876427



Campbell, Bruce CV, et al. "Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): A multicenter, randomized, controlled study." (2018): 328-334.

CONCLUSIONS

- TNK resulted in higher incidence of reperfusion than IV-alteplase before EVT
  - Trial not powered for superiority
  - Predominantly among MCA occlusion patients
  - NNT 8.3 (compared to 15 with alteplase in ECASS-III)
- Safety: No difference
- Cost in U.S: $5800 (TNK) vs $8800 (Alteplase)

Ongoing Tenecteplase Trials

- TWIST (Tenecteplase in Wake-up Ischemic Stroke Trial) study from Norway (NCT03181360).
- TIMELESS study (Tenecteplase in Stroke Patients Between 4.5 and 24 hours) in North America is a phase III, randomized, placebo-controlled trial of IVT in patients presenting within 4.5 and 24 hours from LKW time with ELVO, using perfusion based imaging to assess the efficacy and safety of tenecteplase (NCT03785678).

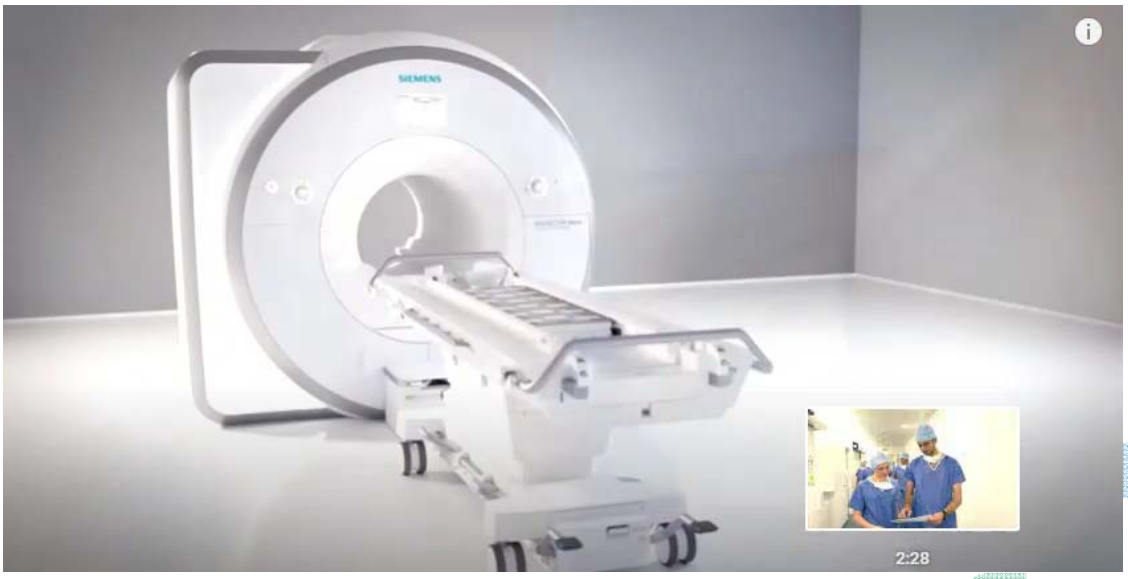
Real World Implications & Unknowns

- How feasible is late window thrombolysis?
- Every PSC may not have MRI or CTP available
- Every CSC may not have MRI techs available 24/7
- Is the benefit of extending late window IVT enough to justify bypassing PSC
- Need for advanced infrastructure
- Do all strokes subtypes benefit the same from late window IVT?

Real World Implication in the US

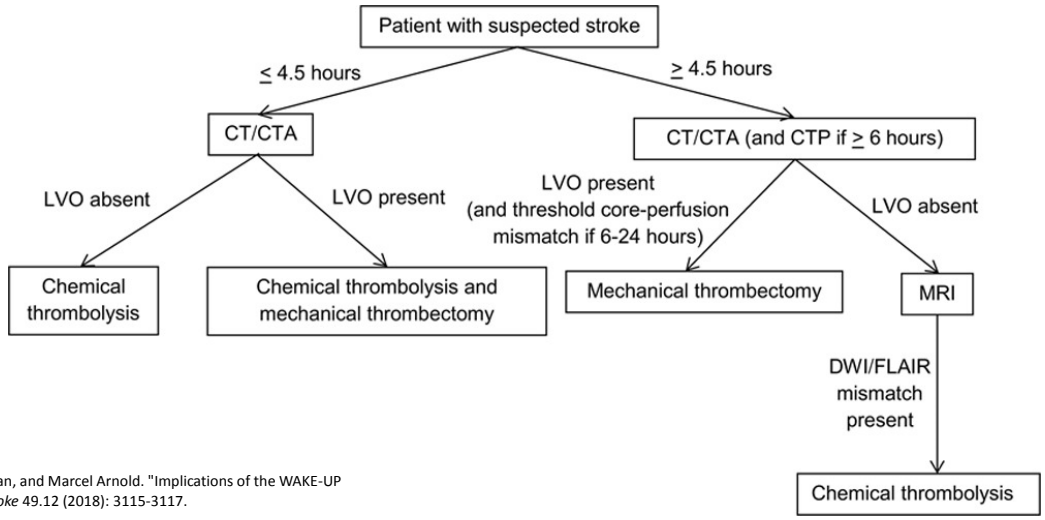
- 136 stroke patients presented and were imaged in the specified time window.
- Of these, 17 (12.5%) received IV tPA.
- Three patients had hemorrhage on 24-h MRI follow up; none had an increase in NIHSS ≥4.
- Of the 119 patients who were screened but not treated, 18 (15%) were eligible based on FLAIR quantitative assessment and 55 (46%) were eligible based on qualitative assessment. In all cases where patients were not treated, there was an identifiable exclusion based on trial criteria.
- During the study period (2016-2018), IV tPA utilization was increased by 5.6% due to screening and treating patients with unknown onset stroke.

Adil, Malik M., et al. "Routine use of FLAIR-negative MRI in the treatment of unknown onset stroke." *Journal of Stroke and Cerebrovascular Diseases* 29.9 (2020): 105093.



https://www.youtube.com/watch?v=hcd3FVdmOxU

Proposed Algorithm of Extended Window IVT



Silver, Brian, and Marcel Arnold. "Implications of the WAKE-UP Trial." *Stroke* 49.12 (2018): 3115-3117.

Summary

- Thrombolysis windows can be extended using tissue-based windows
- The field of acute stroke management is shifting from time-based windows to tissue-based windows
- Both CTP and MRI can help establish infarct core, penumbra and time of onset of symptoms in those with unclear LKW or wake up strokes
- Equally important to know limitations of perfusion imaging
- Real world implication of universal late window thrombolysis will be challenging but should be an option where available
- The ultimate goal is to be able to treat more patients who otherwise may not have been eligible for IVT
- Significantly higher rates of symptomatic hemorrhages in IVT group, however benefits >>risks
- Using more potent thrombolytics may be more efficacious. Studies of tenecteplase ongoing
- Advanced infrastructure changes will be needed to make late window IVT an option at every stroke center

References

- 1. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–1329.
- 2. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012;379:2364–2372.
- 3. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA. 1999;282:2019–2026.
- 4. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379:2352–2363.
- 5. Bluhmki E, Chamorro A, Dávalos A, Machnig T, Sauce C, Wahlgren N, et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. Lancet Neurol. 2009;8:1095–1102.
- 6. Emberson, Jonathan, et al. "Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischemic stroke: a meta-analysis of individual patient data from randomised trials." *The Lancet* 384.9958 (2014): 1929-1935.
- 7. Campbell, Bruce CV, et al. "Extending thrombolysis to 4· 5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data." *The Lancet* 394.10193 (2019): 139-147.
- 8. Thomalla, Götz, et al. "MRI-guided thrombolysis for stroke with unknown time of onset." *New England Journal of Medicine* 379.7 (2018): 611-622.
- 9. Campbell, Bruce CV, et al. "Extending thrombolysis to 4· 5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data." *The Lancet* 394.10193 (2019): 139-147.
- 10. Campbell, Bruce CV, et al. "Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): A multicenter, randomized, controlled study." (2018): 328-334.

Every life deserves world class care.

Thank You!

Email: kharalg@ccf.org