AHA Acute Ischemic Stroke Guidelines

2019 Update to 2018 Guidelines

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12/17/2020

Financial Disclosures

- None

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

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

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

William J. Powers, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, FAHA, Vice Chair; Teri Ackerson, BSN, RN; Opeolu M. Adeoye, MD, MS, FAHA; Nicholas C. Bambakidis, MD, FAHA; Kyra Becker, MD, FAHA; José Biller, MD, FAHA; Michael Brown, MD, MSc; Bart M. Demaerschalk, MD, MSc, FAHA; Brian Hoh, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Chelsea S. Kidwell, MD, FAHA; Thabele M. Leslie-Mazwi, MD; Bruce Ovbiagele, MD, MSc, MAS, MBA, FAHA; Phillip A. Scott, MD, MBA, FAHA; Kevin N. Sheth, MD, FAHA; Andrew M. Southerland, MD, MSc, FAHA; Deborah V. Summers, MSN, RN, FAHA; David L. Tirschwell, MD, MSc, FAHA; on behalf of the American Heart Association Stroke Council

Class (strength) of Recommendation

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**

(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:

- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

Level (Quality) of Evidence

LEVEL A

- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

Prehospital bypass

If eligible for IV-alteplase, the benefit of bypassing the closest IV-alteplase-capable hospital to go to a thrombectomy capable center is uncertain

CLASS IIb (WEAK) **Benefit ≥ Risk**

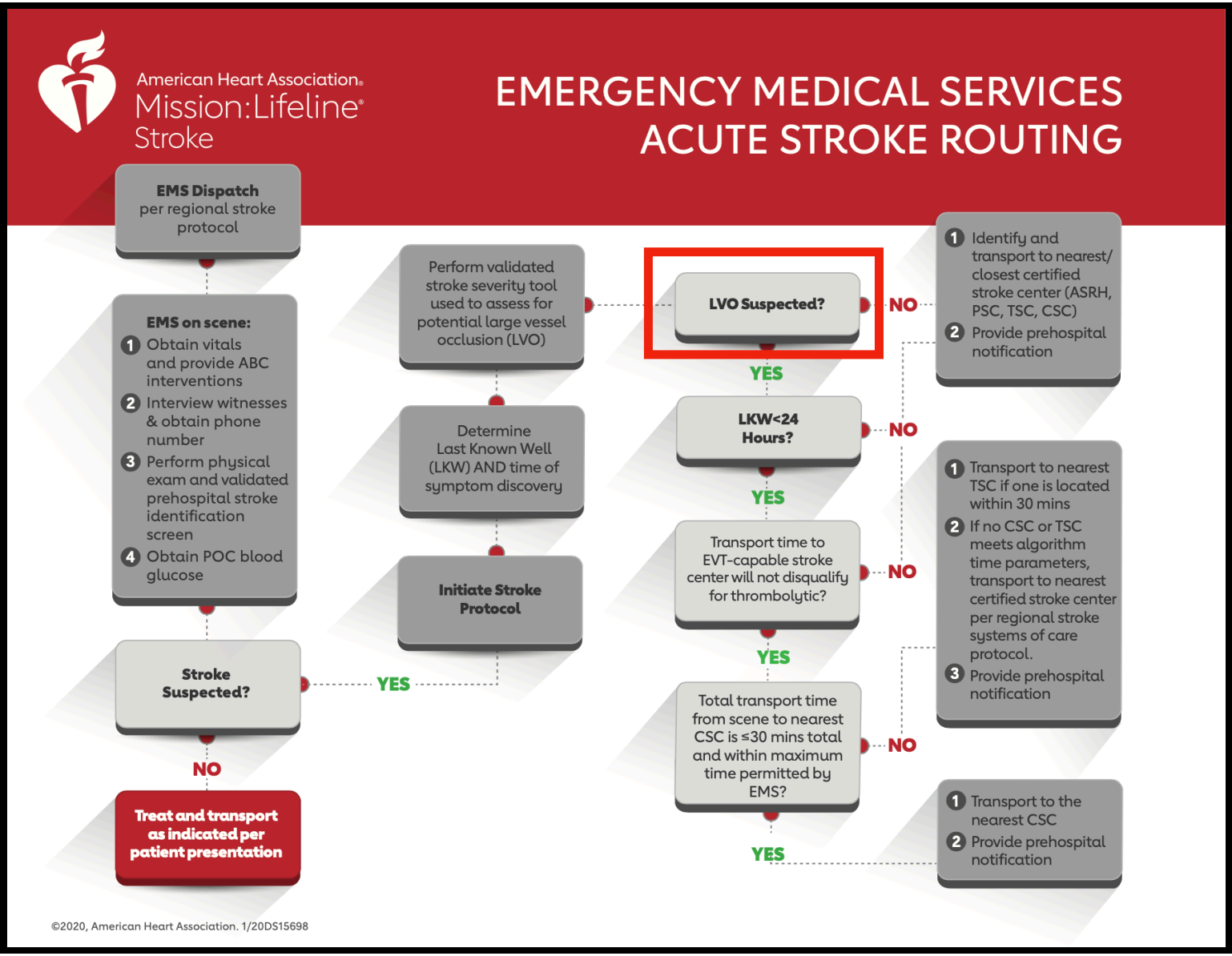
Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

LEVEL B-NR **(Nonrandomized)**

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

AHA also publishes Mission: Lifeline Stoke



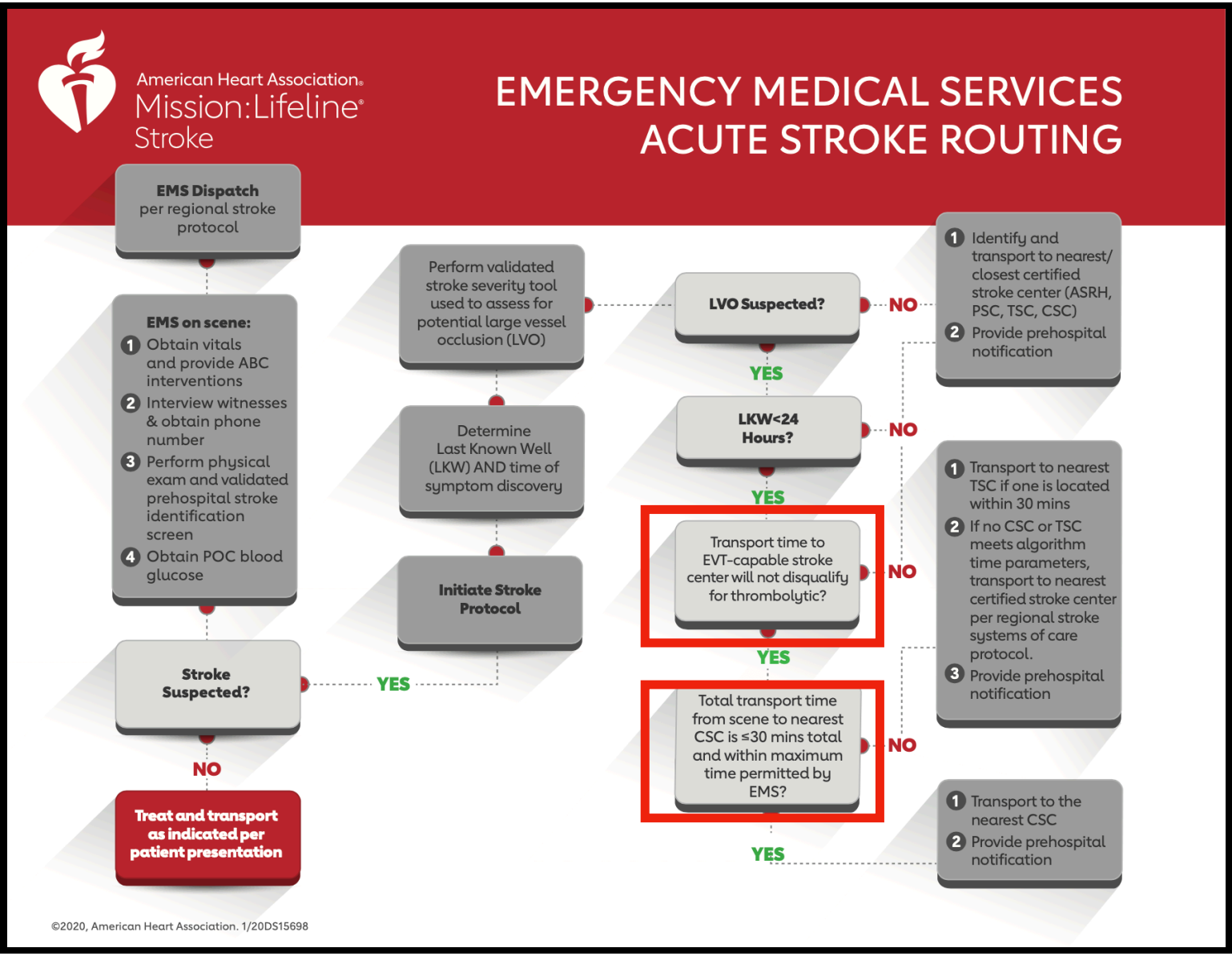
https://www.heart.org/en/professional/quality-improvement/mission-lifeline/mission-lifeline-stroke. Downloaded 9/20/2020

Problem with Stroke Severity Scales

Not accurate enough?

- All scales had Area under the ROC curve was mostly 0.7-0.85
- Probability of LVO with a positive LVO prediction test was thought to be only 50-60%, whereas >10% of those with a negative test may have an LVO
- Thus, more effective tools are needed to identify suspected stroke patients with a strong probability of LVO

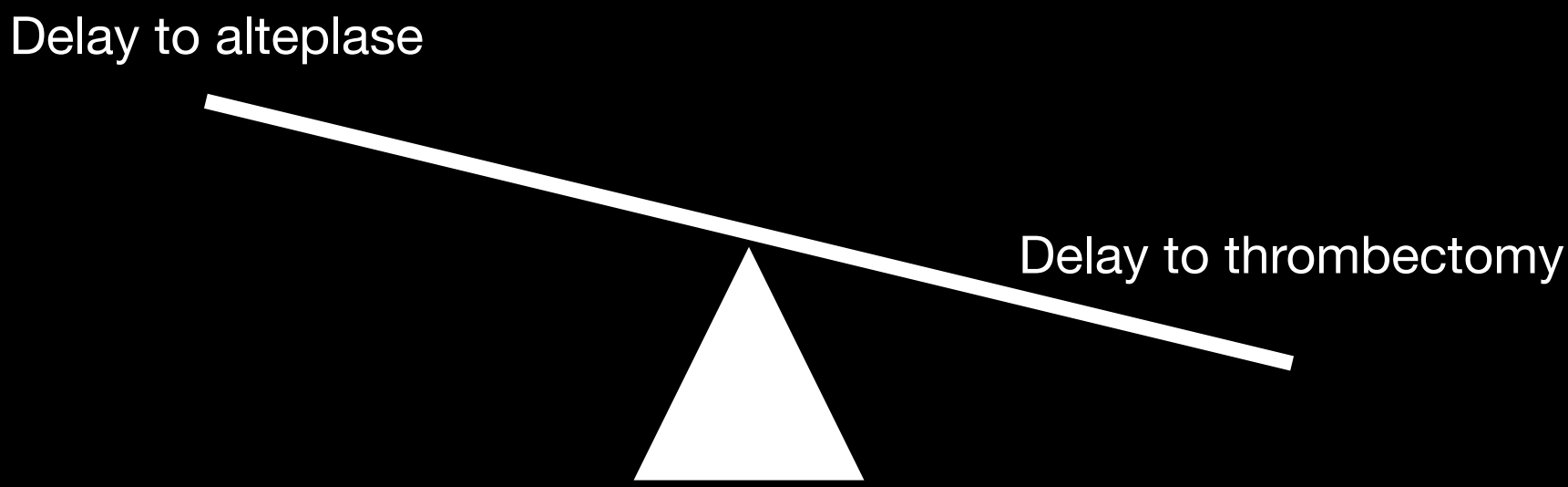
Stroke. 2018;49:e111-e122



https://www.heart.org/en/professional/quality-improvement/mission-lifeline/mission-lifeline-stroke. Downloaded 9/20/2020

Thresholds of additional travel time

Insufficient evidence



Prehospital bypass to healthcare facility able to perform thrombectomy if patient is ineligible for IV thrombolysis while still having strong probability of Large Vessel Occlusion (LVO)

CLASS IIb (WEAK) **Benefit ≥ Risk**

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

LEVEL C-EO **(Expert Opinion)**

Consensus of expert opinion based on clinical experience

Some patients can get alteplase after 4.5 hours from last known well (LKW)

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
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  - It is reasonable to choose treatment A over treatment B

LEVEL B-R **(Randomized)**

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

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*

N Engl J Med 2018; 379:611-622

WAKE-UP Trial

- 503 patients enrolled
- Randomized to Alteplase vs standard care
- 70 centers in 8 European countries

Inclusion

- Ages 18-80
- Last Known well >4.5 hours to infinity, but symptom recognition within 4.5 hours
- Early stroke based on MRI (DWI+ and FLAIR-)

Exclusion

- ICH
- If planned thrombectomy
- NIHSS >25
- Lesion larger than 1/3rd of the territory of the Middle Cerebral artery
- Contraindications to alteplase (other than unknown LKW)

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)

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

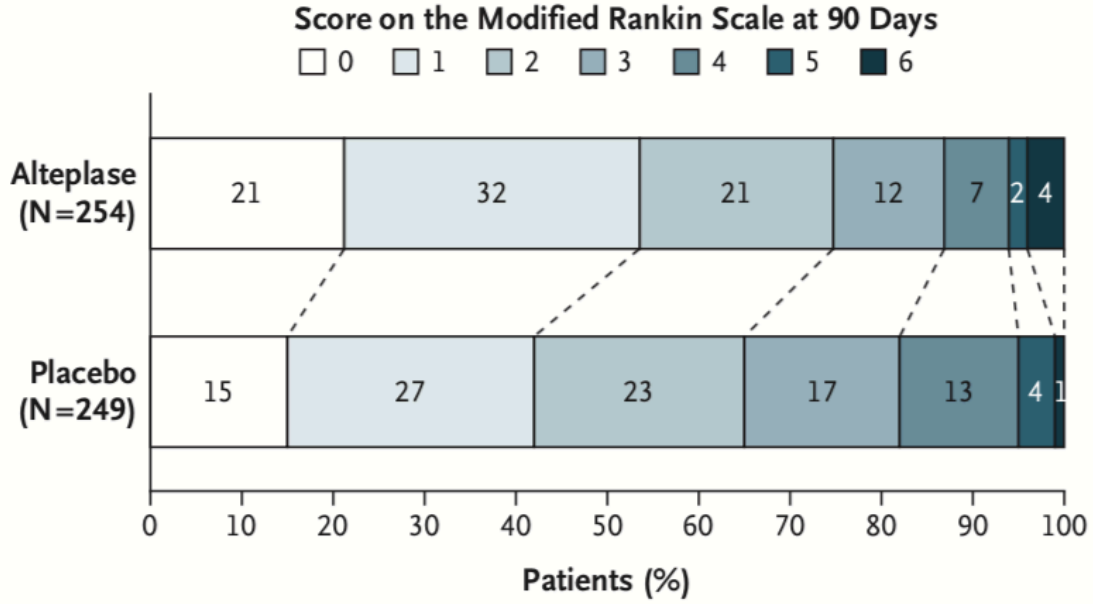


Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

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*

N Engl J Med 2019;380:1795-803

EXTEND Trial

Published May 9, 2019 - too new for current update

- Multicenter RCT in Australia, New Zealand, Taiwan, Finland from 2010-2018
- Double blinded to Alteplase vs placebo
- Stopped early because of WAKE-UP, and only enrolled 225/400

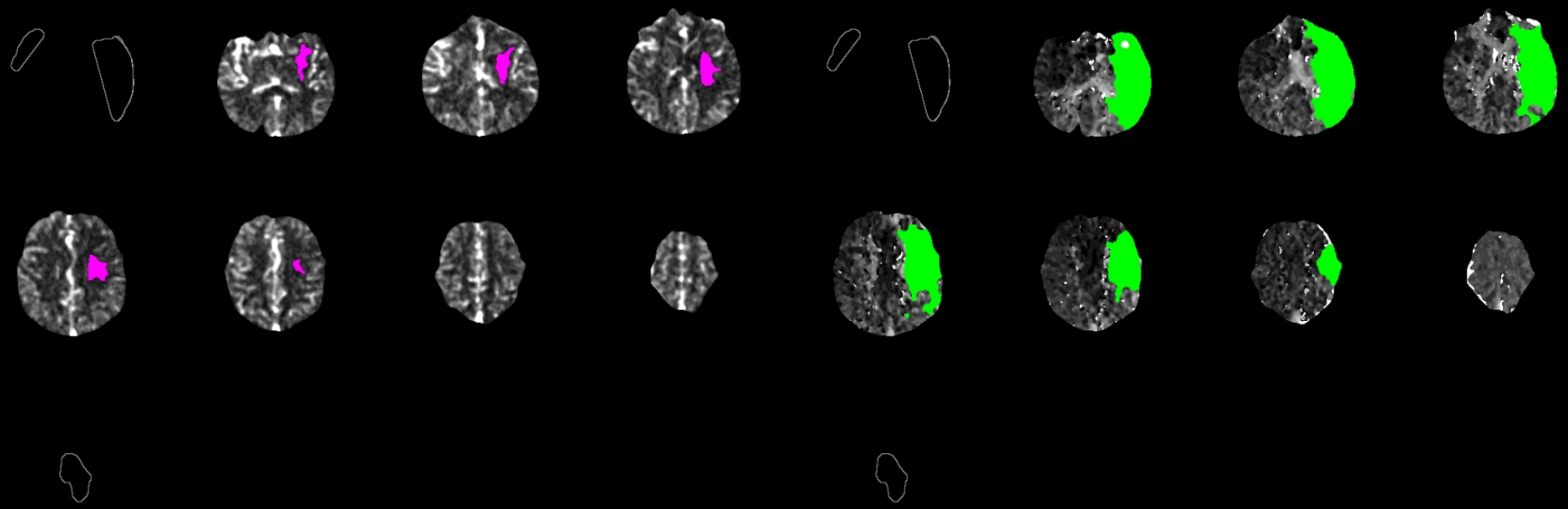
EXTEND Inclusion

- Between 4.5 and 9 hours after stroke onset or on awakening with stroke symptoms
- Hypoperfused but salvageable regions of brain detected on automated perfusion imaging (as processed by RAPID)
  - Perfusion lesion-ischemic core mismatch >1.2
  - Absolue difference in volume >10ml
  - Ischemic-core volume <70ml

EXTEND imaging

- MRI/MR Perfusion
- CTP

Example of CTP



CBF<30% volume: 17 ml

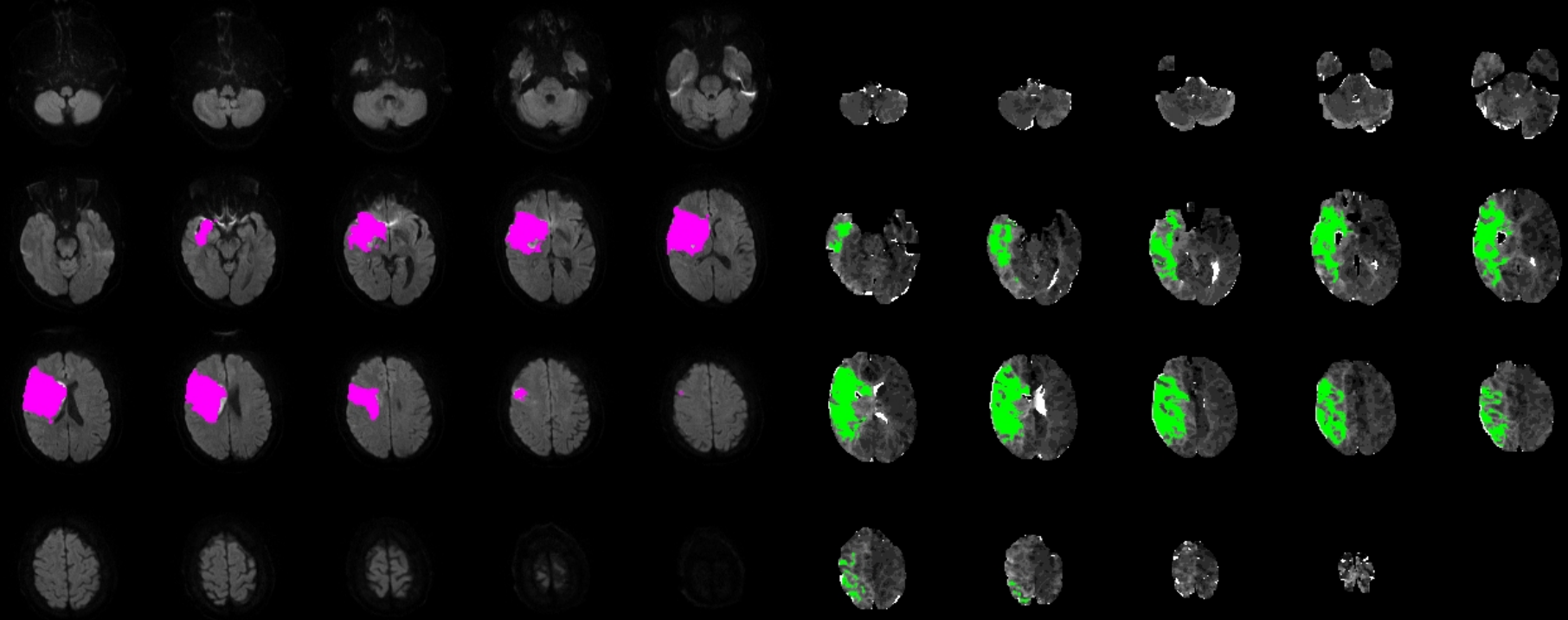
Tmax>6.0s volume: 156 ml

Mismatch volume: 139 ml
Mismatch ratio: 9.2

RAPID

Not for primary diagnosis. Warning: review source data quality and bolus timing.

Example of MRI/MRP



ADC<620 volume: 89 ml

Tmax>6.0s volume: 124 ml

Mismatch volume: 35 ml
Mismatch ratio: 1.4

RAPID

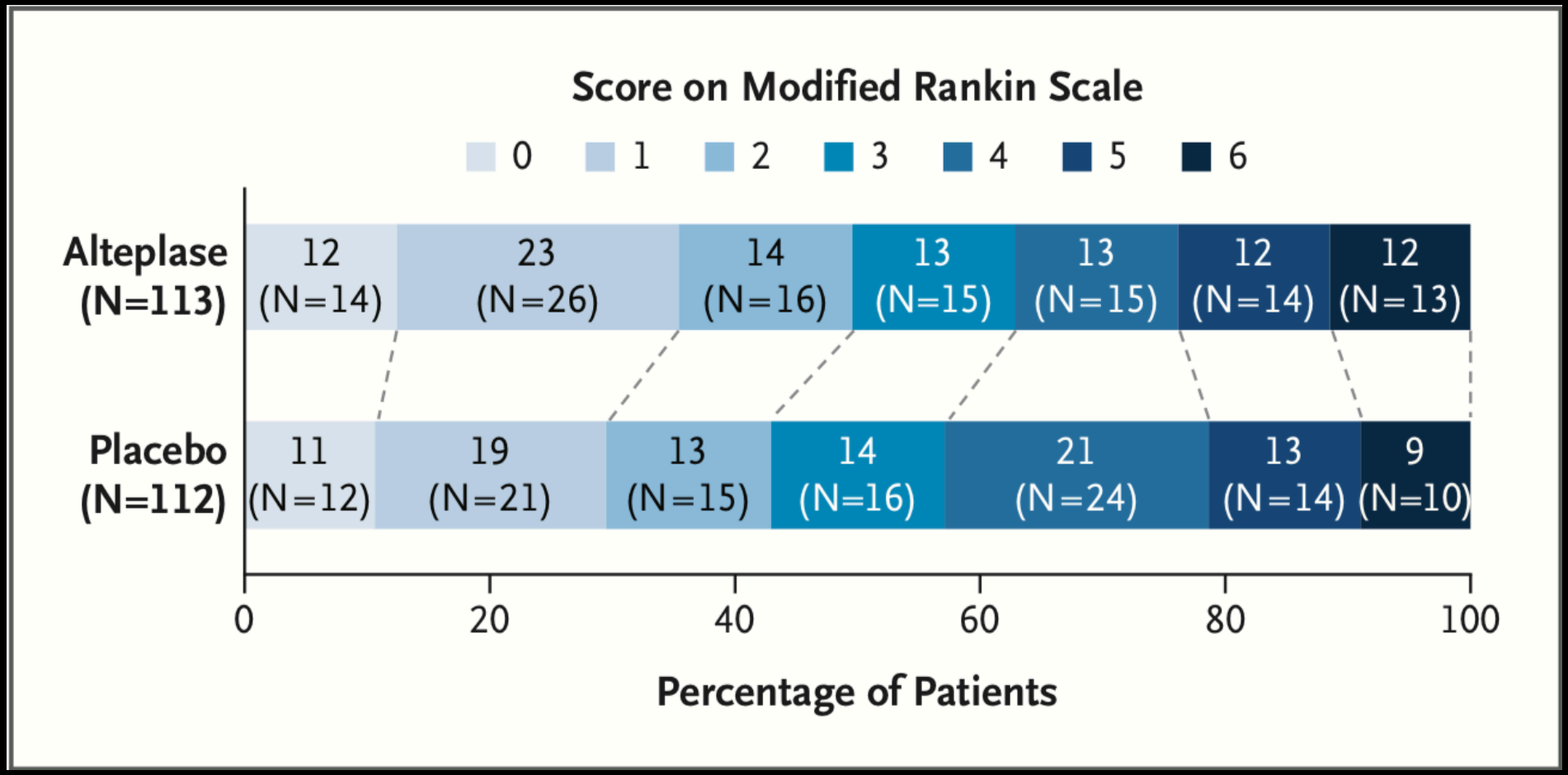
Not for primary diagnosis.

EXTEND Exclusion

- Prestroke mRS >2
- Very severe strokes (NIHSS >26)
- Going for endovascular thrombectomy

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


Score on Modified Rankin Scale
0
1
2
3
4
5
6
Alteplase (N=113)
12 (N=14)
23 (N=26)
14 (N=16)
13 (N=15)
13 (N=15)
12 (N=14)
12 (N=13)
Placebo (N=112)
11 (N=12)
19 (N=21)
13 (N=15)
14 (N=16)
21 (N=24)
13 (N=14)
9 (N=10)
0
20
40
60
80
100
Percentage of Patients

For mild non-disabling strokes (NIHSS 0-5), IV alteplase is not recommended

CLASS III: No Benefit (MODERATE) **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:

- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

LEVEL B-R **(Randomized)**

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

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

JAMA. 2018;320(2):156-166

PRISMS Trial

- Designed for 948 patients in 75 hospitals in the USA
- Phase 3b RCT of Alteplase vs ASA within 3 hours of LKW
- Only 313 patients enrolled at 53 centers
- Stopped early by Sponsor, Genetech “financial decision based on the fact that the trial could not be completed within the allotted funds in the specified time frame.”
- “…Very early study termination precludes any definitive conclusions.”

PRISMS Trial

What is a disabling stroke?

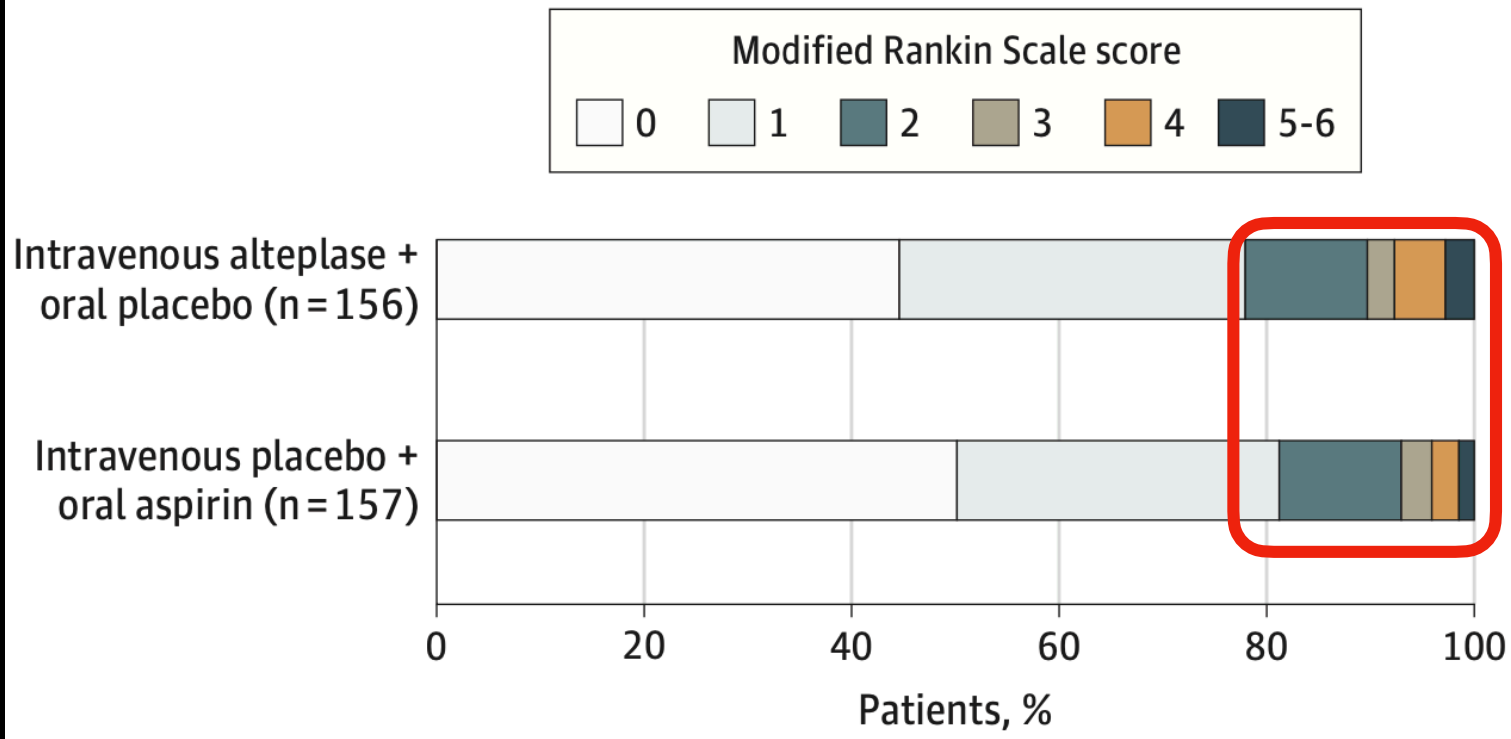
- Unable to perform ADL's or return to work
- Local clinicians made the determination in consultation with patients and available family
- Unable to walk

PRISMS Trial

Exclusion

- Pre-stroke mRS of 2-6
- Dysphagia
- Any contraindication to alteplase

Figure 2. Modified Rankin Scale Score Distributions at 90 Days by Treatment Group



These distributions, which were used for the primary outcome analysis, included imputation for missing 90-day scores.

Tenecteplase may be a reasonable alternative to alteplase in patients eligible for mechanical thrombectomy

CLASS IIb (WEAK) **Benefit ≥ Risk**

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

LEVEL B-R **(Randomized)**

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

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*

N Engl J Med 2018;378:1573-82

EXTEND-IA TNK

- 202 patients over 13 centers in Australia and New Zealand
- Open labeled, blinded-outcome, RCT
- IV Tenectaplase (bolus 0.25mg/kg, max dose 25mg) vs IV alteplase (0.9mg/kg, max dose 90mg, with first 10% given over 60 second, the rest over an hour) in patients about to undergo thrombectomy

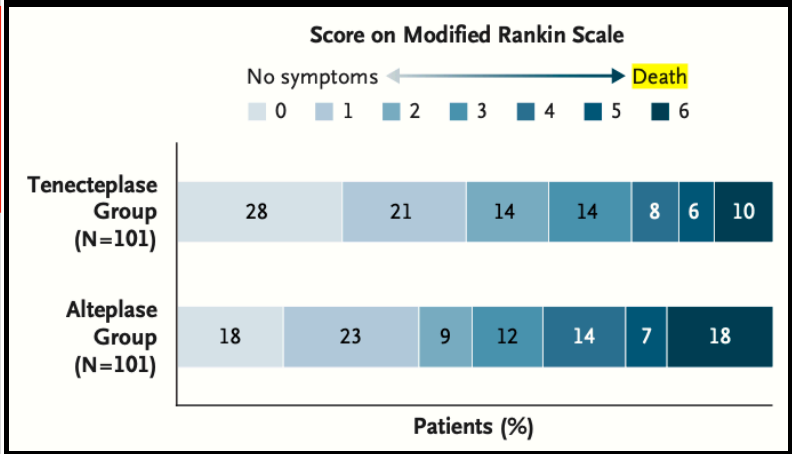
EXTEND-IA TNK

Inclusion

- Candidate for both IV thrombolysis and mechanical thrombectomy within 4.5 hours
- LVO locations were ICA, MCA or basilar
- No upper NIHSS, no upper age limit

Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days†				
Median score (IQR) on ordinal analysis‡	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
Functionally independent outcome — no. (%)§	65 (64)	52 (51)		
Adjusted incidence ratio			1.2 (1.0–1.5)	0.06
Adjusted odds ratio			1.8 (1.0–3.4)	0.06
Excellent outcome — no. (%)§	52 (51)	43 (43)		
Adjusted incidence ratio			1.2 (0.9–1.6)	0.20
Adjusted odds ratio			1.4 (0.8–2.6)	0.23
Early neurologic improvement — no. (%)§¶	72 (71)	69 (68)		
Adjusted incidence ratio			1.0 (0.9–1.2)	0.70
Adjusted odds ratio			1.1 (0.6–2.1)	0.70
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



In patients with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who do not receive IV alteplase, aspirin plus clopidogrel started within 24 hours after symptom onset and continued for 21 days, can reduce recurrent ischemic stroke risk for up

CLASS I (STRONG) **Benefit >>> Risk**

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

LEVEL A

- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

Upgraded from IIa;B-R in original 2018 Guideline

ORIGINAL ARTICLE

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

Yongjun Wang, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., David Wang, D.O., F.A.H.A., F.A.A.N., Chunxue Wang, M.D., Ph.D., Chen Wang, M.D., Hao Li, Ph.D., Xia Meng, M.D., Ph.D., Liying Cui, M.D., Ph.D., Jianping Jia, M.D., Ph.D., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jinsheng Zeng, M.D., Ph.D., Yansheng Li, M.D., Ph.D., Zhimin Wang, M.D., Haiqin Xia, M.D., and S. Claiborne Johnston, M.D., Ph.D., for the CHANCE Investigators*

N Engl J Med 2013;369:11-19

CHANCE Trial

- RCT at 114 clinical centers in China
- 5,170 patients with mild stroke (NIHSS <4) or TIA
- Both groups got open label ASA (75-300mg per day at the discretion of the treating physician) for **21** days
- Treatment arm received 300mg load of clopidogrel on day one, then 75mg/day to 90 days
- Started within 24 hours of symptom onset

Table 2. Efficacy and Safety Outcomes.

Outcome	Aspirin (N=2586)		Clopidogrel and Aspirin (N=2584)		Hazard Ratio (95% CI)	P Value
	Patients with Event *no.*	Event Rate %	Patients with Event *no.*	Event Rate %		
Primary outcome						
Stroke	303	11.7	212	8.2	0.68 (0.57–0.81)	<0.001
Secondary outcomes						
Stroke, myocardial infarction, or death from cardiovascular causes	307	11.9	216	8.4	0.69 (0.58–0.82)	<0.001
Ischemic stroke	295	11.4	204	7.9	0.67 (0.56–0.81)	<0.001
Hemorrhagic stroke	8	0.3	8	0.3	1.01 (0.38–2.70)	0.98
Myocardial infarction	2	0.1	3	0.1	1.44 (0.24–8.63)	0.69
Death from cardiovascular causes	5	0.2	6	0.2	1.16 (0.35–3.79)	0.81
Death from any cause	10	0.4	10	0.4	0.97 (0.40–2.33)	0.94
Transient ischemic attack	47	1.8	39	1.5	0.82 (0.53–1.26)	0.36
Safety outcomes						
Bleeding*						
Severe	4	0.2	4	0.2	0.94 (0.24–3.79)	0.94
Moderate	4	0.2	3	0.1	0.73 (0.16–3.26)	0.68
Mild	19	0.7	30	1.2	1.57 (0.88–2.79)	0.12
Any bleeding	41	1.6	60	2.3	1.41 (0.95–2.10)	0.09

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 19, 2018 VOL. 379 NO. 3

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

S. Claiborne Johnston, M.D., Ph.D., J. Donald Easton, M.D., Mary Farrant, M.B.A., William Barsan, M.D., Robin A. Conwit, M.D., Jordan J. Elm, Ph.D., Anthony S. Kim, M.D., Anne S. Lindblad, Ph.D., and Yuko Y. Palesch, Ph.D., for the Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators*

N Engl J Med 2018;379:215-25

POINT Trial

- 4,881 patients North America, Europe, Australia, and New Zealand (82.8% enrolled in the USA)
- Enrolled within 12 hours of mild stroke (NIHSS <4 or high risk TIA (ABCD2 score of 4 or more)
- RCT with clopidogrel 600mg load, followed by 75mg/day for 90 days. Everyone received ASA at discretion of treating physician (recommended 162 for 5 days, followed by 81mg daily)
- Excluded patients going to get anticoagulation

Table 2. Efficacy and Safety Outcomes.

Outcome	Clopidogrel plus Aspirin (N=2432)	Aspirin (N=2449)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary efficacy outcome				
Composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes	121 (5.0)	160 (6.5)	0.75 (0.59–0.95)	0.02
Secondary efficacy outcomes				
Ischemic stroke	112 (4.6)	155 (6.3)	0.72 (0.56–0.92)	0.01*
Myocardial infarction	10 (0.4)	7 (0.3)	1.44 (0.55–3.78)	0.46*
Death from ischemic vascular causes	6 (0.2)	4 (0.2)	1.51 (0.43–5.35)	0.52*
Ischemic or hemorrhagic stroke	116 (4.8)	156 (6.4)	0.74 (0.58–0.94)	0.01*
Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage	141 (5.8)	167 (6.8)	0.84 (0.67–1.05)	0.13*
Primary safety outcome				
Major hemorrhage	23 (0.9)	10 (0.4)	2.32 (1.10–4.87)	0.02
Other safety outcomes				
Hemorrhagic stroke	5 (0.2)	3 (0.1)	1.68 (0.40–7.03)	0.47
Symptomatic intracerebral hemorrhage	2 (0.1)	2 (0.1)	1.01 (0.14–7.14)	0.99
Other symptomatic intracranial hemorrhage	2 (0.1)	0		0.16
Major hemorrhage other than intracranial hemorrhage	17 (0.7)	7 (0.3)	2.45 (1.01–5.90)	0.04
Minor hemorrhage	40 (1.6)	13 (0.5)	3.12 (1.67–5.83)	<0.001
Death from any cause	18 (0.7)	12 (0.5)	1.51 (0.73–3.13)	0.27

Why were these DAPT trial successful when others weren’t before

- Particularly high risk of recurrent strokes (Enrolled within the first 24 hours)
- Low risk for hemorrhage (Less severe strokes and TIA’s)

For patients within 6-16 hours of LKW who have LVO in the anterior circulation and meet DAWN or DEFUSE 3 eligibility, mechanical thrombectomy is recommended

CLASS I (STRONG) **Benefit >>> Risk**

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

LEVEL A

- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

New in 2018, but not new in update

The DAWN Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

N Engl J Med 2018; 378:11-21

The DAWN Trial

- 206 patients enrolled (planned for 500)
- **Multicenter, prospective, RCT**, Bayesian adaptive-enrichment design, and **blinded assessment of endpoints**
- **Industry sponsored**
  - Authors had unrestricted access to the data
  - analysis was performed by data-management staff from Styker, with oversight from independent statisticians

Missmatch (clinical symptoms vs imaging core infarct)

- Prestroke mRS <2
- LVO present in intracranial ICA or M1
- RAPID software to determine infarct volume
  - Age ≥80, NIHSS >10, Infarct <21ml
  - Age <80, NIHSS >10, Infarct <31ml
  - Age <80, NIHSS >20, Infarct 31-51ml

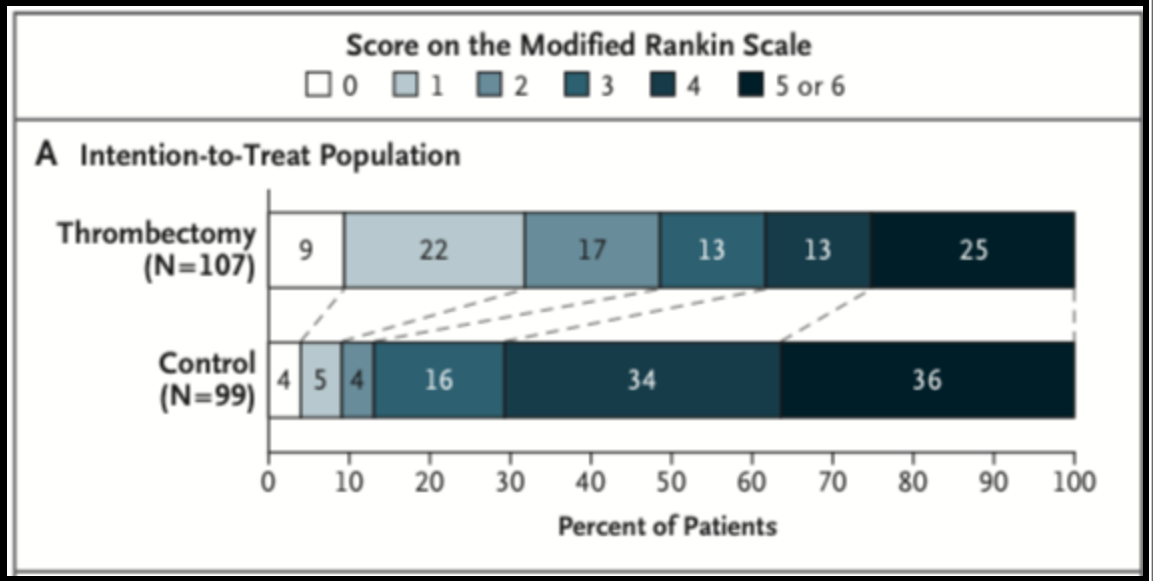
Imaging needed in DAWN Trial

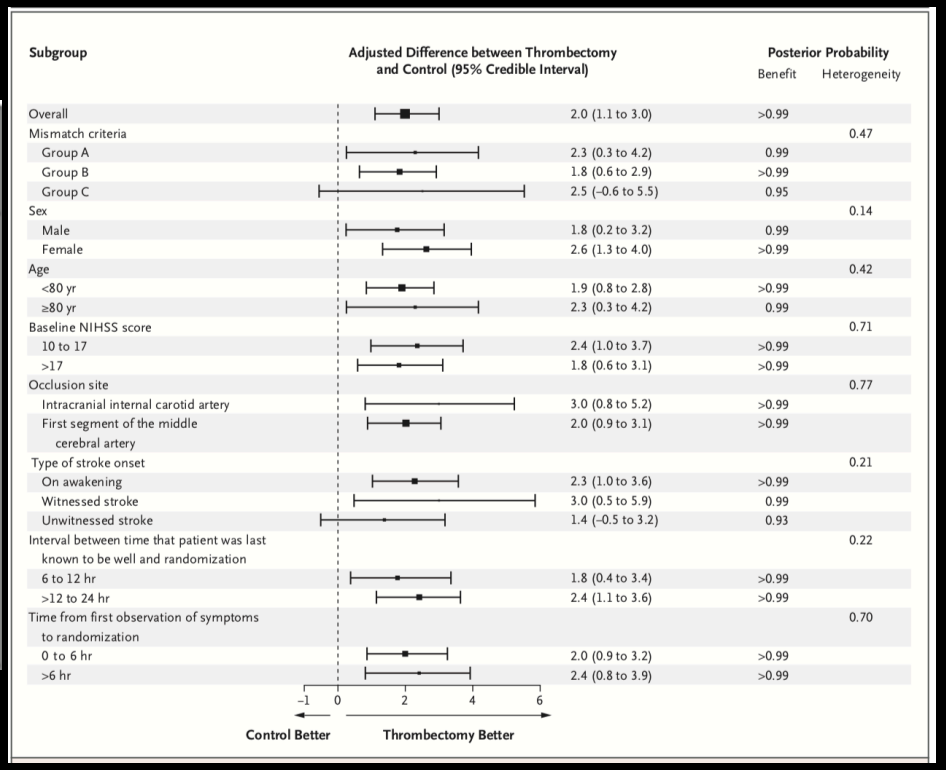
- MRI (diffusion weighted sequences)
  - Area where ADC is <620 is considered infarcted
- CTP
  - Area where CBF is <30% is considered infarcted

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			

NNT of 3





Subgroup	Adjusted Difference between Thrombectomy and Control (95% Credible Interval)	Posterior Probability: Benefit	Posterior Probability: Heterogeneity
Overall	2.0 (1.1 to 3.0)	>0.99	
Mismatch criteria			0.47
Group A	2.3 (0.3 to 4.2)	0.99	
Group B	1.8 (0.6 to 2.9)	>0.99	
Group C	2.5 (−0.6 to 5.5)	0.95	
Sex			0.14
Male	1.8 (0.2 to 3.2)	0.99	
Female	2.6 (1.3 to 4.0)	>0.99	
Age			0.42
<80 yr	1.9 (0.8 to 2.8)	>0.99	
≥80 yr	2.3 (0.3 to 4.2)	0.99	
Baseline NIHSS score			0.71
10 to 17	2.4 (1.0 to 3.7)	>0.99	
>17	1.8 (0.6 to 3.1)	>0.99	
Occlusion site			0.77
Intracranial internal carotid artery	3.0 (0.8 to 5.2)	>0.99	
First segment of the middle cerebral artery	2.0 (0.9 to 3.1)	>0.99	
Type of stroke onset			0.21
On awakening	2.3 (1.0 to 3.6)	>0.99	
Witnessed stroke	3.0 (0.5 to 5.9)	0.99	
Unwitnessed stroke	1.4 (−0.5 to 3.2)	0.93	
Interval between time that patient was last known to be well and randomization			0.22
6 to 12 hr	1.8 (0.4 to 3.4)	>0.99	
>12 to 24 hr	2.4 (1.1 to 3.6)	>0.99	
Time from first observation of symptoms to randomization			0.70
0 to 6 hr	2.0 (0.9 to 3.2)	>0.99	
>6 hr	2.4 (0.8 to 3.9)	>0.99	

Table 3. Safety Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)	Risk Ratio (95% CI)
	no. (%)		*percentage points*	
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		

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*

N Engl J Med 2018; 378:708-718

DEFUSE 3

- 38 US centers for 182 patients
- Endovascular therapy + medical therapy vs medical therapy alone
- Sponsored by the NIH
- Any FDA thrombectomy device was used

DEFUSE 3

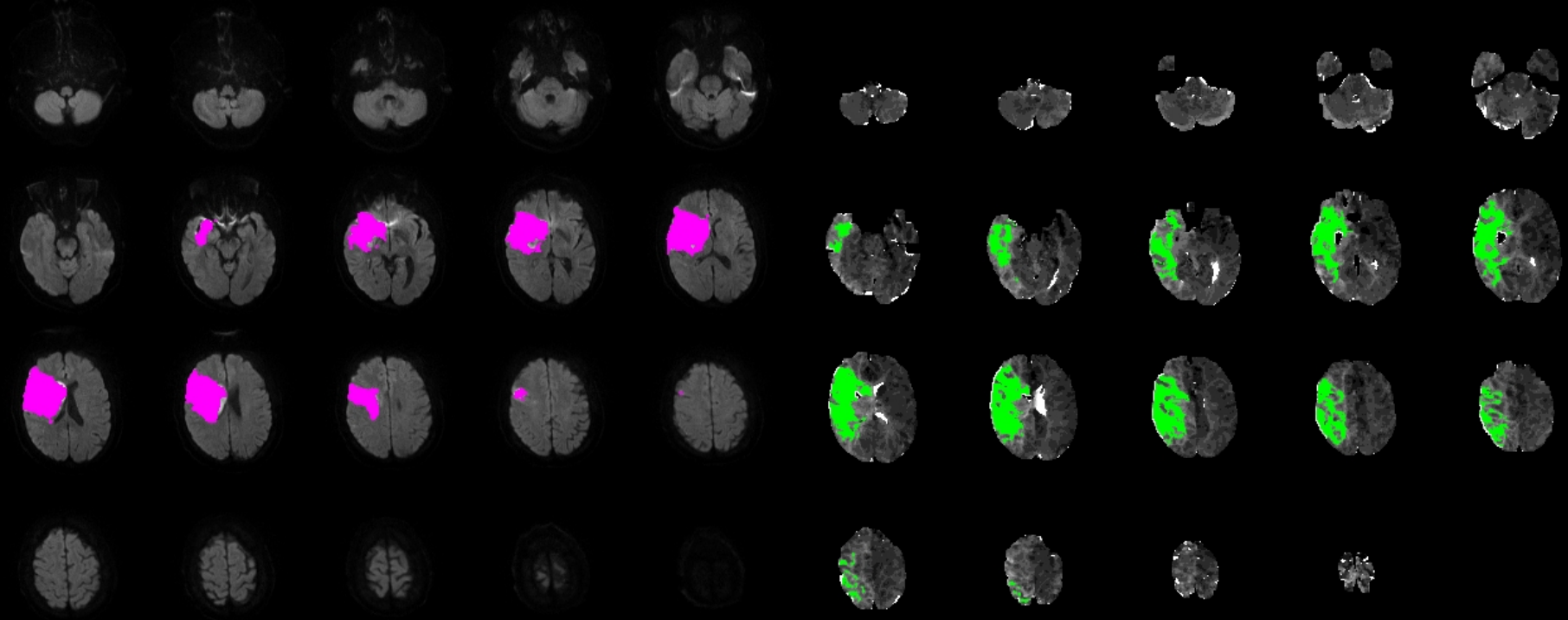
Inclusion

- If NCCT done, ASPECT score ≥6
- LVO present in M1 or LVO
- Pre-stroke mRS 0-2
- Infarct core <70ml
- Ratio of ischemia to infarction of 1.8
- Absolute volume of penumbra of 15ml or more

DEFUSE 3 imaging

- MRI/MR Perfusion
- CTP

Example of MRI/MRP



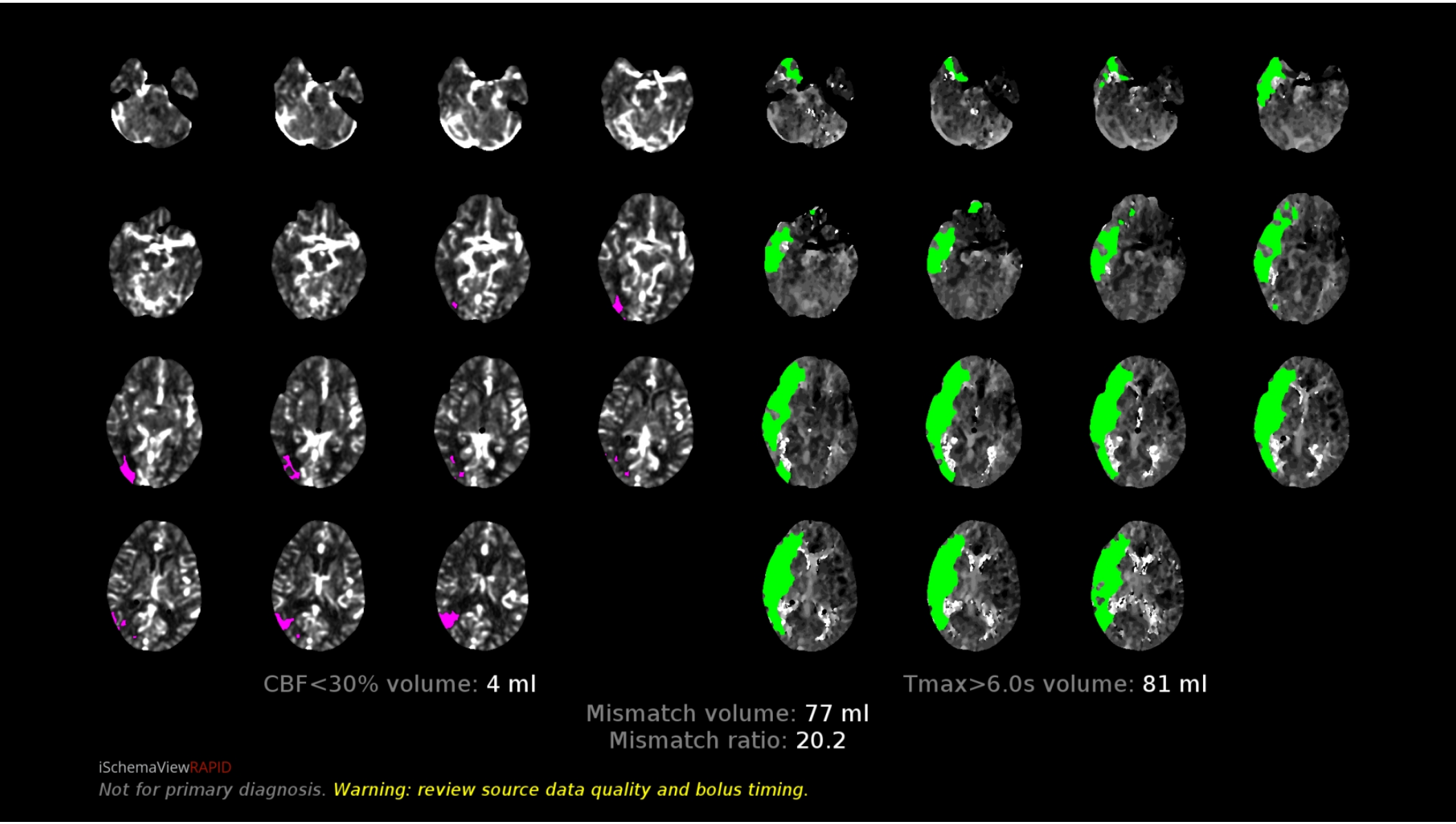
ADC<620 volume: 89 ml

Tmax>6.0s volume: 124 ml

Mismatch volume: 35 ml
Mismatch ratio: 1.4

RAPID

Not for primary diagnosis.


CBF<30% volume: 4 ml
Tmax>6.0s volume: 81 ml
Mismatch volume: 77 ml
Mismatch ratio: 20.2
iSchemaViewRAPID
Not for primary diagnosis. Warning: review source data quality and bolus timing.

Results

- Enrolled 182/476 patients, but stopped early in light of DAWN trial results (Per NIH)

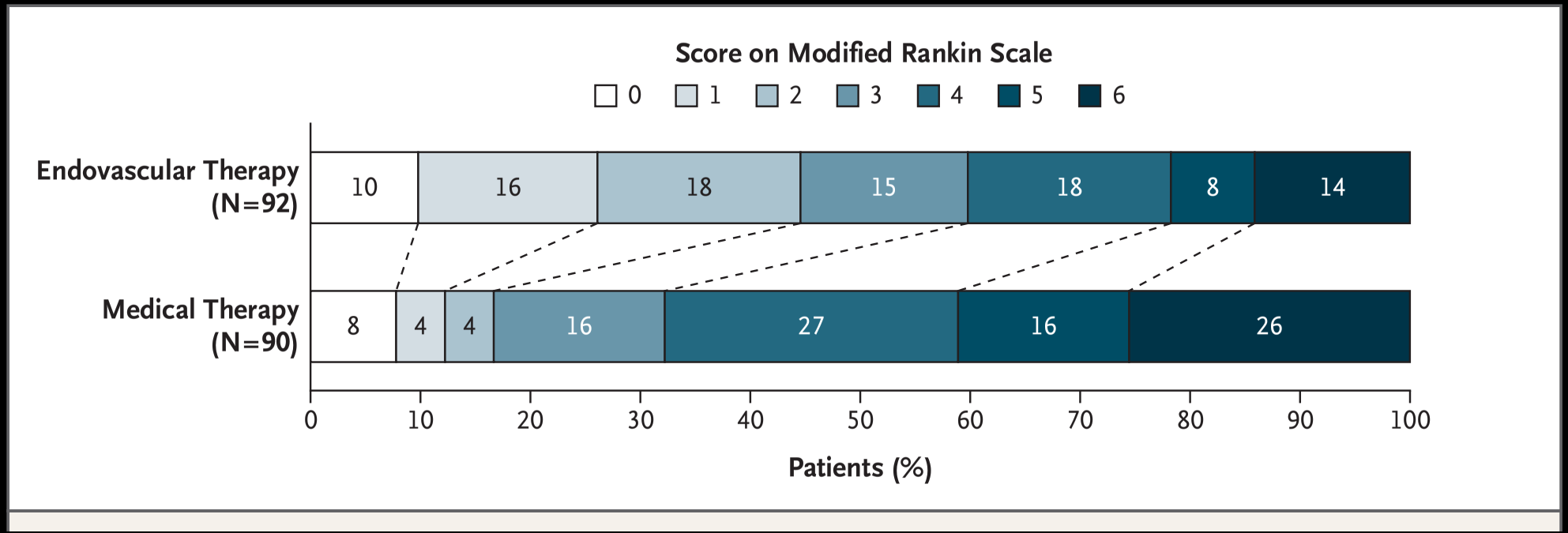

Score on Modified Rankin Scale
0
1
2
3
4
5
6
Endovascular Therapy (N=92)
10
16
18
15
18
8
14
Medical Therapy (N=90)
8
4
4
16
27
16
26
0
10
20
30
40
50
60
70
80
90
100
Patients (%)

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
Imaging outcomes**				
Median infarct volume at 24 hr (IQR) — ml	35 (18–82)	41 (25–106)	—	0.19
Median infarct growth at 24 hr (IQR) — ml	23 (10–75)	33 (18–75)	—	0.08
Reperfusion >90% at 24 hr — no./total no. (%)	59/75 (79)	12/67 (18)	4.39 (2.60–7.43)	<0.001
Complete recanalization at 24 hr — no./total no. (%)	65/83 (78)	14/77 (18)	4.31 (2.65–7.01)	<0.001
TICI score of 2b or 3 — no./total no. (%)	69/91 (76)	—	—	

NNT 4

For patients within 16-24 hours of LKW who have LVO in anterior circulation and meet DAWN eligibility, mechanical thrombectomy is reasonable

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

LEVEL B-R **(Randomized)**

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

New in 2018, but not new in update

Summary of recommendations

- Prehospital Stroke Severity Scales are good, but not as good as we want
- Prehospital bypass in potential cases of LVO involves delays to alteplase vs delays to thrombectomy. Local decision.
- If alteplase out of the question, then OK to bypass if likely LVO present
- MRI imaging can find patient eligible for alteplase >4.5 hours after LKW
- Avoid alteplase in non-disabling mild strokes
- Consider about tenectaplase in LVO cases
- DAPT within 24 hours and continued for 21 days after mild stroke or TIA to reduce risk of recurrent stroke
- Advanced imaging can find patients eligible for EVT up to 24 hours after LKW

Some secondary stroke prevention if we have time

MRI is reasonable in some patients to provide additional information to guide secondary stroke prevention

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

LEVEL C-EO **(Expert Opinion)**

Consensus of expert opinion based on clinical experience

In nondisabling (mRS 0-2) AIS in the carotid territory who are candidates for CEA or stenting, noninvasive imaging of the cervical carotid arteries should be performed routinely within 24 hours of admission

CLASS I (STRONG) **Benefit >>> Risk**

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

LEVEL B-NR **(Nonrandomized)**

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

Intracranial vessel imaging is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention treatments.

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

LEVEL C-EO **(Expert Opinion)**

Consensus of expert opinion based on clinical experience

Effectiveness of prolonged cardiac monitoring during hospitalization after AIS to guide treatment selection for prevention of recurrent stroke is uncertain

CLASS IIb (WEAK) **Benefit ≥ Risk**

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

LEVEL C-LD **(Limited Data)**

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

Echocardiography is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

LEVEL C-EO **(Expert Opinion)**

Consensus of expert opinion based on clinical experience

For patients who have a non-cardioembolic AIS while taking anti platelet therapy, switching to warfarin is not indicated for secondary stroke prevention

CLASS III: No Benefit (MODERATE) **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:

- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

LEVEL B-NR **(Nonrandomized)**

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

For patients with AIS who qualify for statin treatment, in-hospital initiation of statin therapy is reasonable

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

LEVEL C-LD **(Limited Data)**

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

Starting or restarting antihypertensives during hospitalization in patients with BP >140/90 who are neurologically stable is safe and is reasonable to improve long-term BP control unless contraindicated

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

LEVEL B-R **(Randomized)**

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

Smokers with AIS should receive in-hospital initiation of high-intensity behavioral interventions to promote smoking cessation. Also, OK to use nicotine replacement therapy .

CLASS I (STRONG) **Benefit >>> Risk**

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

LEVEL A

- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

For smokers with an AIS, in-hospital initiation of varenicline to promote smoking cessation might be considered

CLASS IIb (WEAK) **Benefit ≥ Risk**

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

LEVEL B-R **(Randomized)**

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs