Thrombectomy performed in an extended time window

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Articles

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

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Article Info

Summary Full Text Tables and Figures References Supplementary Material

Summary

Background

In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations included.

Methods

We formed the HERMES collaboration to pool patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) done between December, 2010, and December, 2014. In these trials, patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days. By direct access to the study databases, we extracted

HERMES review

HERMES

2016 meta-analysis of ischaemic stroke trials performed 2010 to 2015:

1. MR CLEAN
2. ESCAPE
3. REVASCAT
4. SWIFT PRIME
5. EXTEND IA

Results:

- 1287 participants. Median age 68. Equal gender.
- site of occlusion – ICA 21%, M1 69% and M2 8%.
- symptom onset to reperfusion - median 285 min (210-362 m)

Conclusions:

- Significantly reduced disability at 90 days v. control

- Mortality at 90 days and risk of IC bleed did not differ between populations.

- ✓ Ischaemic stroke of proximal arterial circulation on CTA or MRA
- ✓ Symptom onset <6hours
- ✓ Use of second generation neurothrombectomy devices + standard care (Intervention) vs standard care (control).
- ✓ Modified Rankin Score assessment at 90 days.

The DAWN trial (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

ABSTRACT

BACKGROUND

The effect of endovascular thrombectomy that is performed more than 6 hours after the onset of ischemic stroke is uncertain. Patients with a clinical deficit that is disproportionately severe relative to the infarct volume may benefit from late thrombectomy.

METHODS

We enrolled patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume, with mismatch criteria defined according to age (<80 years or ≥80 years). Patients were randomly assigned to thrombectomy plus standard care (the thrombectomy group) or to standard care alone (the control group). The coprimary end points were the mean score for disability on the utility-weighted modified Rankin scale (which ranges from 0 [death] to 10 [no symptoms or disability]) and the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability) at 90 days.

RESULTS

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jovin at the University of Pittsburgh Medical Center Stroke Institute, Department of Neurology, Presbyterian University Hospital, 200 Lothrop St., C-400, Pittsburgh, PA 15217, or at jovintg@upmc.edu.

*A complete list of sites and investigators in the DAWN trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Nogueira and Jovin contributed equally to this article.

This article was published on November 11, 2017, at NEJM.org.

DOI: 10.1056/NEJMoa1706442

DAWN

Multicenter, randomised and blinded outcome assessment trial. Trial ceased early. NEJM - Jan 2018.

Endovascular therapy plus medical therapy v medical therapy alone in patients with mismatch between deficit and infarct.

Patient eligibility:

- ✓ **Previously well with onset of symptoms 6-24 hours to reperfusion**
- ✓ **Mismatch between the severity of the clinical deficyt and infarct volume (NIHSS score v infarct volume).**
- ✓ **CTA or MRA with an occlusion of proximal MCA or intracranial carotid**

Results:

- ✓ **206 patients. Median age 70. Gender equal.**
- ✓ **Site of occlusion: ICA + MCA**
- ✓ **NIHSS score - median 17. Median infarct volume 7.6ml.**
- ✓ **Symptom onset to reperfusion – 6-12hrs (55%) 12-24hrs (43%)**

Conclusions:

- ✓ **Favourable shift in function outcomes on the modified Rankin Scale at 90d with significant reduction in severe disability and death (25% v 42%)**
- ✓ **No significant increase in serious adverse events.**
- ✓ **Number needed to treat to achieve an additional 1 functional point on modified Rankin score - 2.8.**

Limitations:

- ✓ **Patient enrolments were restricted to those with small or medium volume infarcts.**

Protocol

International Journal of Stroke WSO

A multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3)

International Journal of Stroke
0(0) 1–10

DOI: 10.1177/1747493017701147
journals.sagepub.com/home/wso
SAGE

Gregory W Albers[1], Maarten G Lansberg[1], Stephanie Kemp[1], Jenny P Tsai[1], Phil Lavori[1], Soren Christensen[1], Michael Mlynash[1], Sun Kim[1], Scott Hamilton[1], Sharon D Yeatts[2], Yuko Palesch[2], Roland Bammer[1], Joe Broderick[3] and Michael P Marks[1]

Abstract

Rationale: Early reperfusion in patients experiencing acute ischemic stroke is effective in patients with large vessel occlusion. No randomized data are available regarding the safety and efficacy of endovascular therapy beyond 6 h from symptom onset.

Aim: The aim of the study is to demonstrate that, among patients with large vessel anterior circulation occlusion who have a favorable imaging profile on computed tomography perfusion or magnetic resonance imaging, endovascular therapy with a Food and Drug Administration 510 K-cleared mechanical thrombectomy device reduces the degree of disability three months post stroke.

Design: The study is a prospective, randomized, multicenter, phase III, adaptive, blinded endpoint, controlled trial. A maximum of 476 patients will be randomized and treated between 6 and 16 h of symptom onset.

Procedures: Patients undergo imaging with computed tomography perfusion or magnetic resonance diffusion/perfusion, and automated software (RAPID) determines if the Target Mismatch Profile is present. Patients who meet both clinical and imaging selection criteria are randomized 1:1 to endovascular therapy plus medical management or medical management alone. The individual endovascular therapist chooses the specific device (or devices) employed.

Study outcomes: The primary endpoint is the distribution of scores on the modified Rankin Scale at day 90. The secondary endpoint is the proportion of patients with modified Rankin Scale 0–2 at day 90 (indicating functional independence).

Analysis: Statistical analysis for the primary endpoint will be conducted using a normal approximation of the Wilcoxon–Mann–Whitney test (the generalized likelihood ratio test).

Keywords

Acute ischemic stroke, clinical trial, endovascular, brain imaging, recanalization, imaging based selection

Received: 8 January 2017; accepted: 1 March 2017

Introduction

Endovascular stroke therapy, the removal of blood clots

DEFUSE3

Multicenter, randomised and blinded outcome assessment trial. NEJM - Jan 2018.

Endovascular therapy plus medical therapy v medical therapy alone.

Patient eligibility:

1. Previously well with onset of symptoms 6-16 hours to reperfusion
2. CTA or MRA with:
   a. Infarct volume <70ml
   b. Ratio of ischaemic tissue to infarct volume 1.8
   c. Potential reversible ischaemia of 15ml>
d. Occlusion of proximal MCA or intracranial carotid

Results:

182 patients. Median age 70. Gender equal.

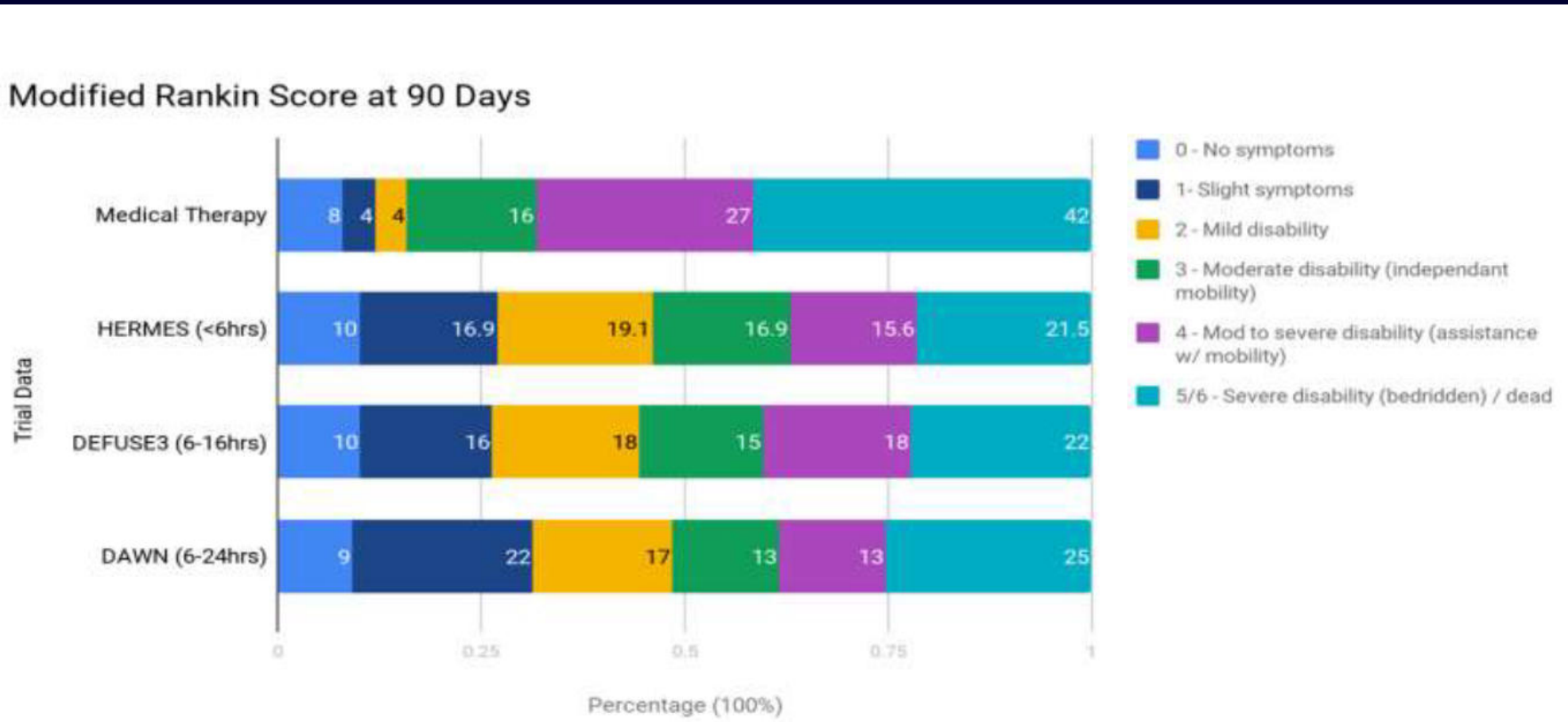
Site of occlusion: internal carotid (35%) and MCA (65%).

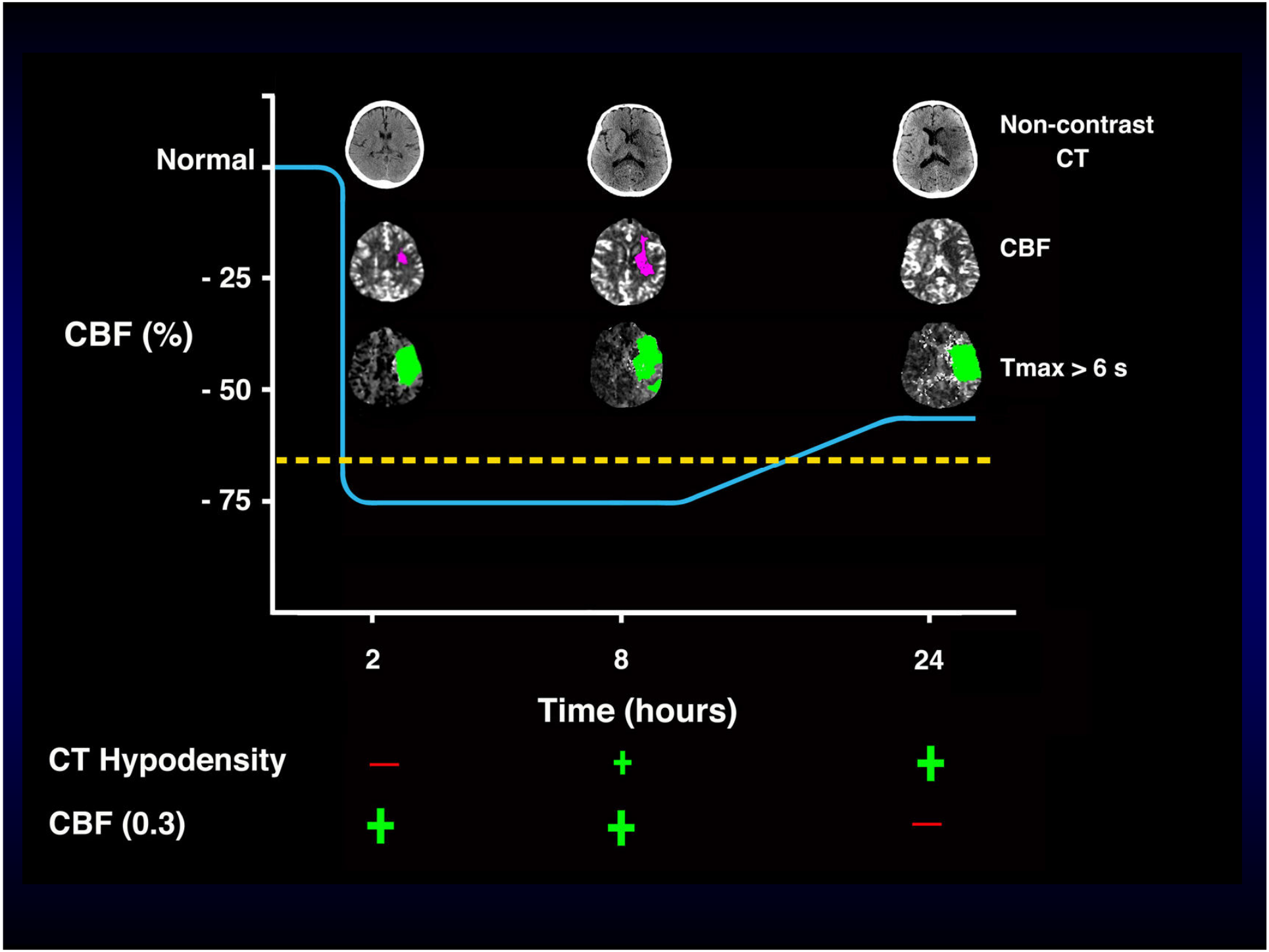
Symptom onset to reperfusion - med 12.05hrs (9.14- 14.06hrs)

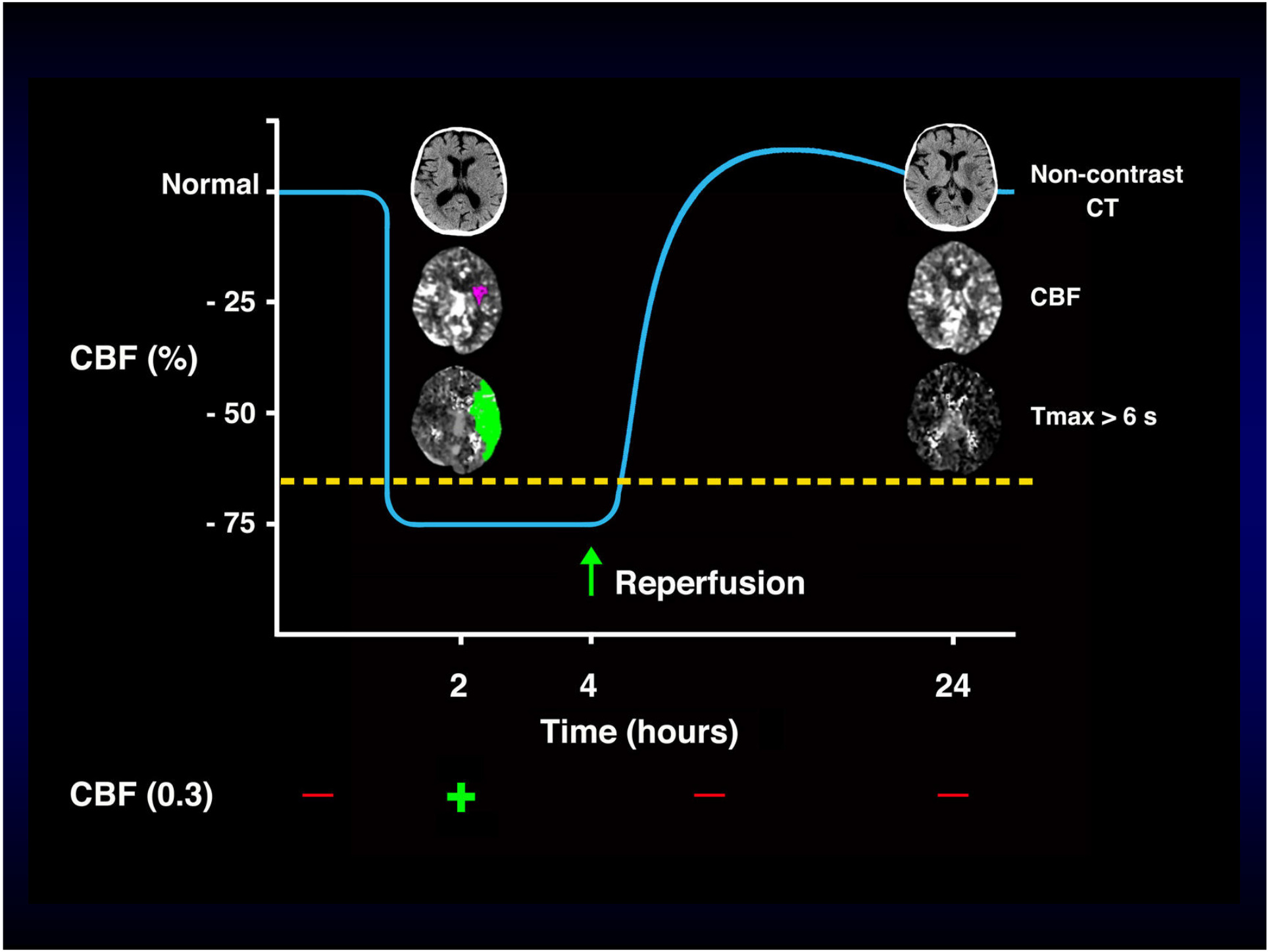
Conclusions:

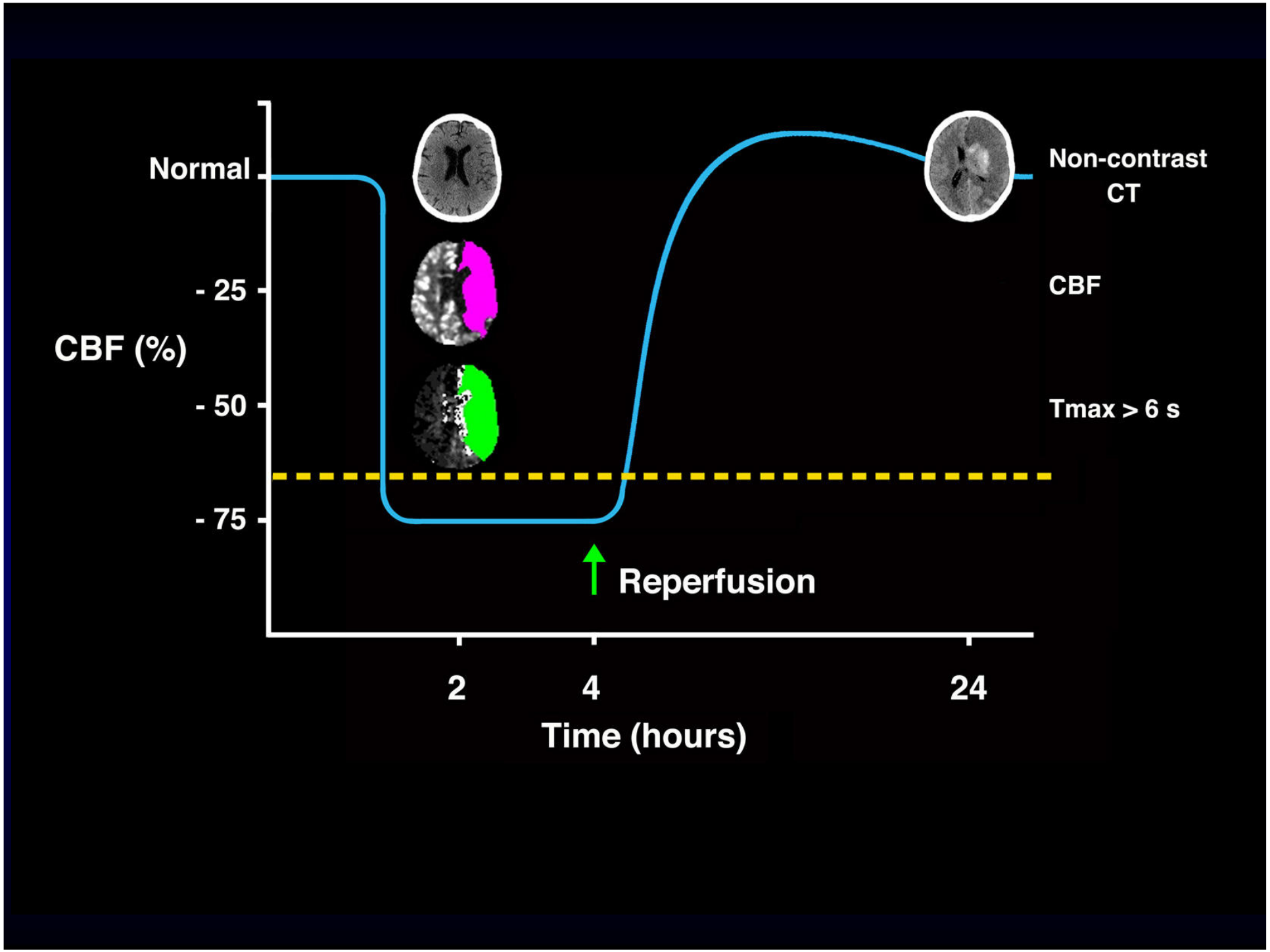
Favourable shift in function outcomes on the mRs at 90d with reduced mortality (14% v 26%).

No significant increase in serious adverse events.


Modified Rankin Score at 90 Days
Trial Data
Medical Therapy
HERMES (<6hrs)
DEFUSE3 (6-16hrs)
DAWN (6-24hrs)
8
4
4
16
27
42
10
16.9
19.1
16.9
15.6
21.5
10
16
18
15
18
22
9
22
17
13
13
25
0
0.25
0.5
0.75
1
Percentage (100%)
0 - No symptoms
1- Slight symptoms
2 - Mild disability
3 - Moderate disability (independant mobility)
4 - Mod to severe disability (assistance w/ mobility)
5/6 - Severe disability (bedridden) / dead


Normal
- 25
- 50
- 75
CBF (%)
Non-contrast CT
CBF
Tmax > 6 s
2
8
24
Time (hours)
CT Hypodensity
CBF (0.3)


Normal
- 25
- 50
- 75
CBF (%)
Non-contrast CT
CBF
Tmax > 6 s
Reperfusion
2
4
24
Time (hours)
CBF (0.3)
–
+
–
–


Normal
- 25
- 50
- 75
CBF (%)
Non-contrast CT
CBF
Tmax > 6 s
Reperfusion
2
4
24
Time (hours)

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

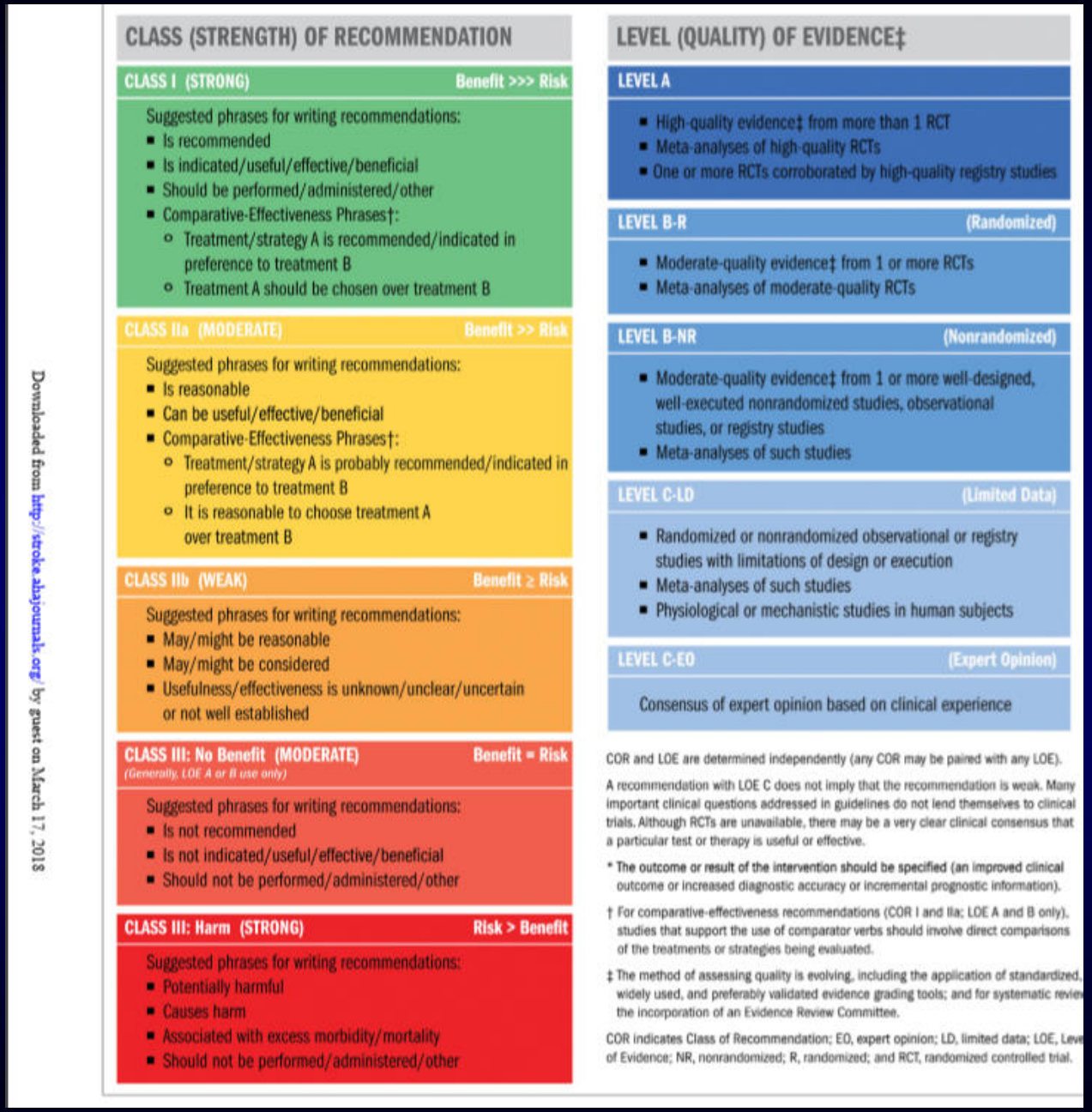
Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Endorsed by the Society for Academic Emergency Medicine

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; Deborah V. Summers, MSN, RN, FAHA; David L. Tirschwell, MD, MSc, FAHA; on behalf of the American Heart Association Stroke Council

Background and Purpose—The purpose of these guidelines is to provide an up-to-date comprehensive set of recommendations for clinicians caring for adult patients with acute arterial ischemic stroke in a single document. The intended audiences are prehospital care providers, physicians, allied health professionals, and hospital administrators. These guidelines supersede the 2013 guidelines and subsequent updates.

Methods—Members of the writing group were appointed by the American Heart Association Stroke Council's Scientific Statements Oversight Committee, representing various areas of medical expertise. Strict adherence to the American Heart Association conflict of interest policy was maintained. Members were not allowed to participate in discussions or to vote on topics relevant to their relations with industry. The members of the writing group unanimously approved all recommendations except when relations with industry precluded members voting. Prerelease review of the draft guideline was performed by 4 expert peer reviewers and by the members of the Stroke Council's Scientific Statements Oversight



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

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic revie the incorporation of an Evidence Review Committee.

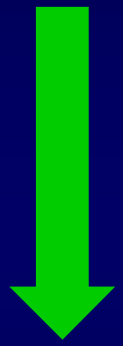
COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Leve of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

3.7. Mechanical Thrombectomy

3.7. Mechanical Thrombectomy	COR	LOE	New, Revised, or Unchanged
1. Patients eligible for IV alteplase should receive IV alteplase even if EVTs are being considered.	I	A	Recommendation reworded for clarity from 2015 Endovascular. See Table LXXXIII in online Data Supplement 1 for original wording.
2. In patients under consideration for mechanical thrombectomy, observation after IV alteplase to assess for clinical response should not be performed.	III: Harm	B-R	Recommendation revised from 2015 Endovascular.
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.
4. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs.	IIb	B-R	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE revised. See Table LXXXIII in online Data Supplement 1 for original wording.
5. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.	IIb	C-EO	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
6. Although its benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1). Additional randomized trial data are needed.	IIb	B-R	Recommendation unchanged from 2015 Endovascular.

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 6 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.
The DAWN trial used clinical imaging mismatch (a combination of NIHSS score and imaging findings on CTP or DW-MRI) as eligibility criteria to select patients with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in function outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33%; 95% CI, 21–44; posterior probability of superiority >0.999).[108] In DAWN, there were few strokes with witnessed onset (12%).The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67; 95% CI, 1.60–4.48; $P<0.0001$).[109] Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN and DEFUSE-3 eligibility should be strictly adhered to in clinical practice.			See Table XXIII in online Data Supplement 1.
9. The technical goal of the thrombectomy procedure should be reperfusion to a modified Thrombolysis in Cerebral Infarction (mTICI) 2b/3 angiographic result to maximize the probability of a good functional clinical outcome.	I	A	Recommendation reworded for clarity from 2015 Endovascular. See Table LXXXIII in online Data Supplement 1 for original wording.

TIME WINDOW



MR/CT

TISSUE WINDOW

Thank you for your attention !