Endovascular Stroke Treatment Updates

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Houston, Texas, 2022

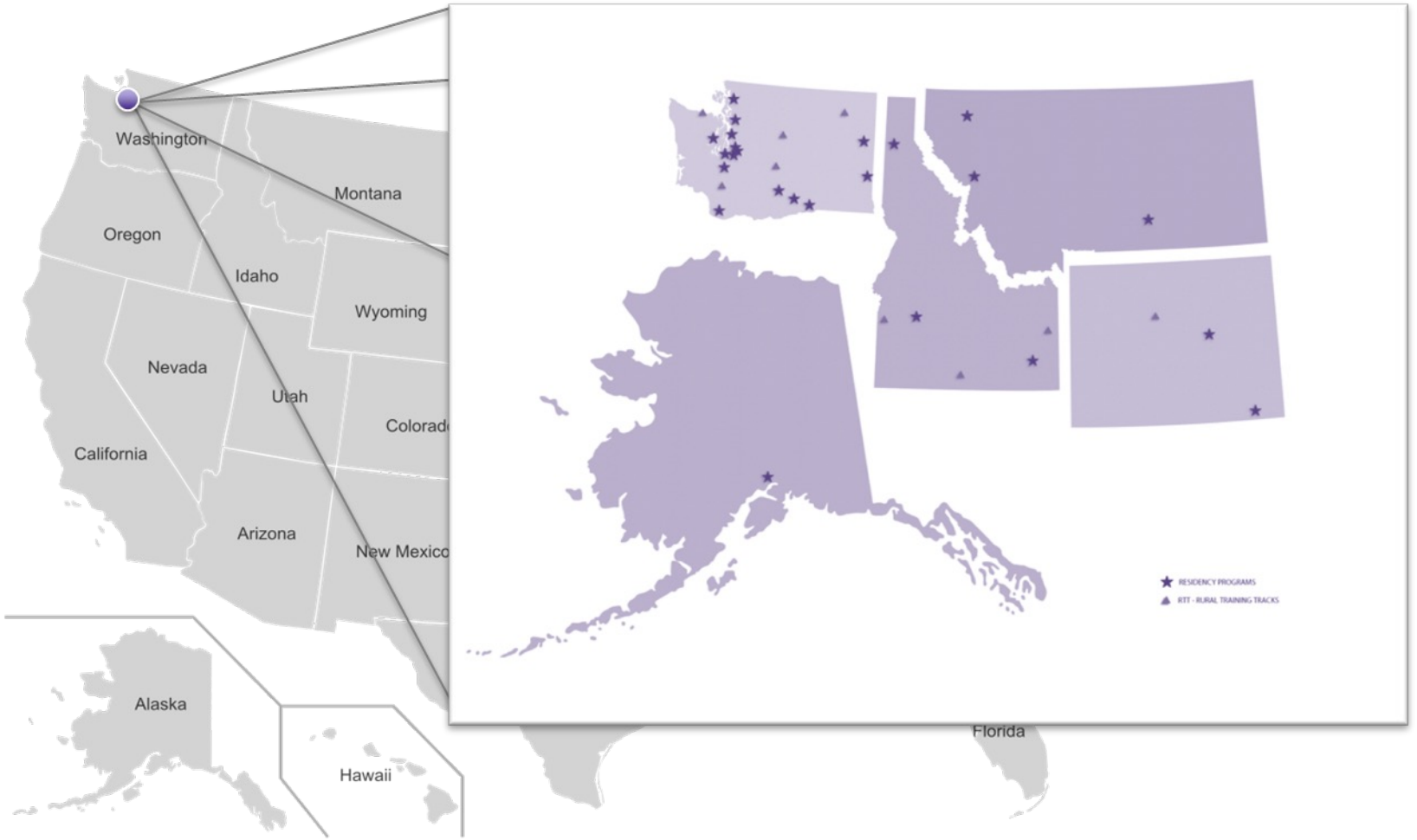
Disclosures

DSMB: ENDOLOW, DISTALS

CEC: REACT, WE-TRUST, PROST, ReCCLAIM II

Texan Map of the USA

We Bring Greetings From Seattle



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We Bring Greetings From Seattle

Seattle Children's Hospital

Harborview Medical Center

UW Montlake Medical Center

UW Northwest Hospital

VA Puget Sound

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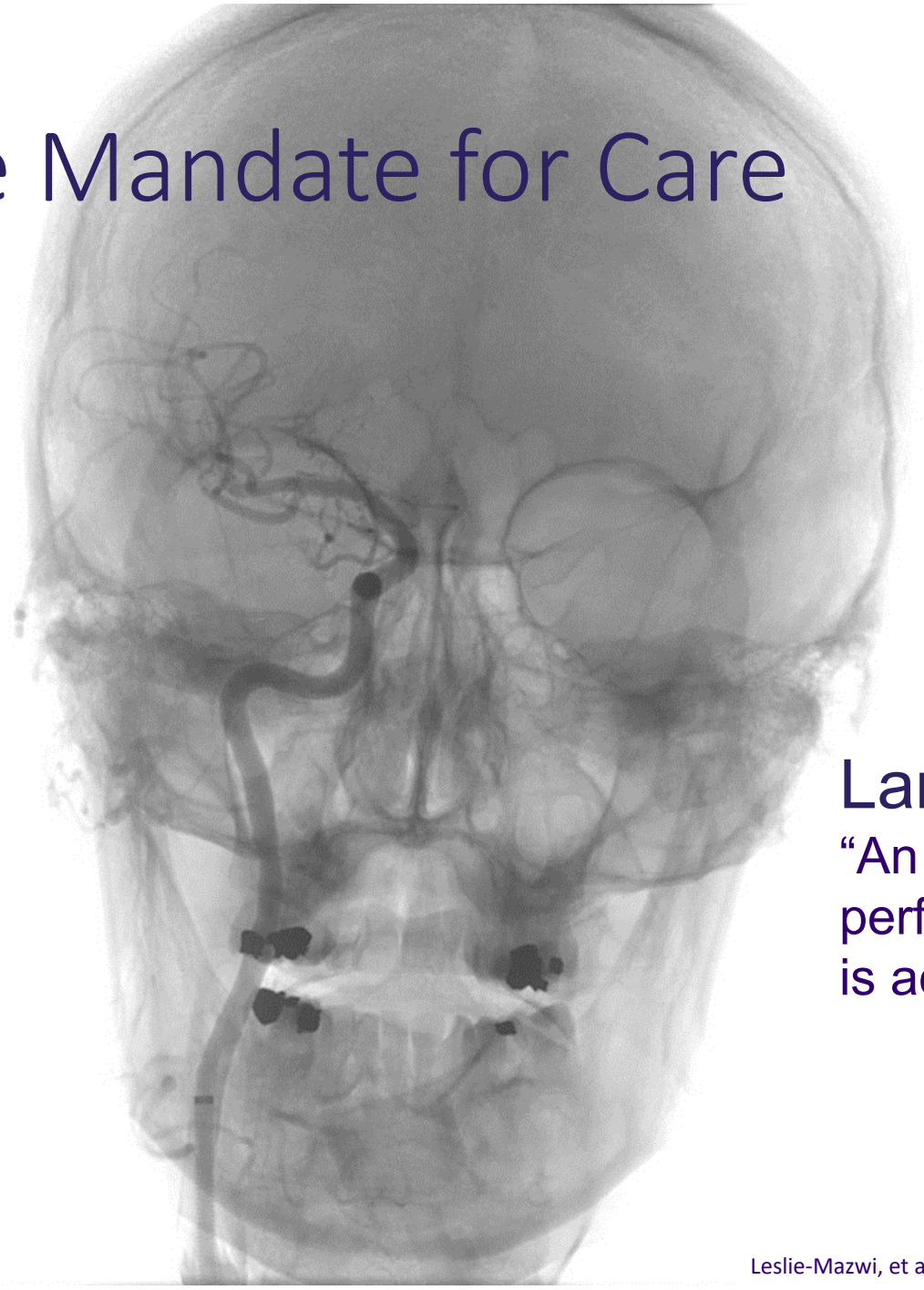
The Mandate for Care



Large Vessel Occlusion (LVO) Stroke

"An acute vascular occlusion that impairs cerebral perfusion, results in significant clinical deficit, and is accessible for endovascular thrombectomy."

Leslie-Mazwi, et al, JNIS 2018

We've Been Asked to Talk About Advances

We will focus on contextualized Randomized Controlled Trials (RCTs), because RCTs have the impact to change universal practice

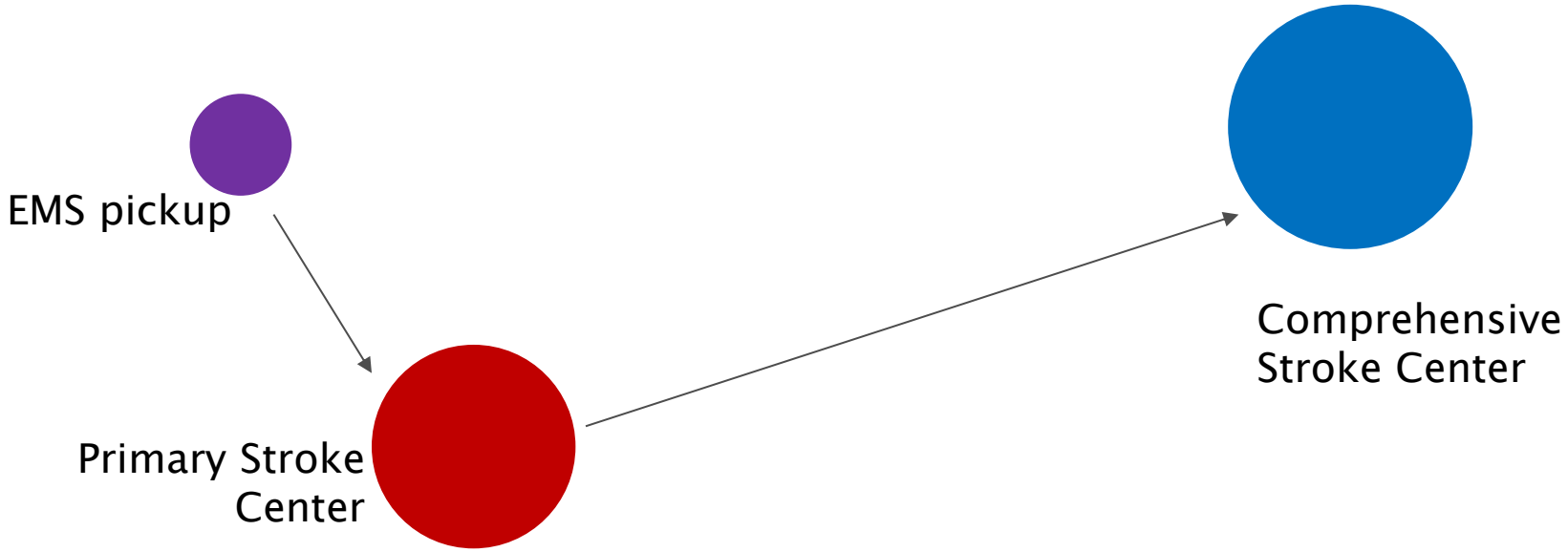
Agenda

We have RCTs recently published now in the following domains impacting endovascular stroke care:

- Triage
- Thrombolytic therapy
- Thrombectomy
  - Selection
  - Reperfusion

STROKE TRIAGE

Current State



This is a strong system for delivering IV tPA.
How do we improve it for patients needing more?

Mohamad et al, ESJ, 2016
Jayaraman et al, JNIS 2016
Parikh NS, et al, Stroke 2018

How Should EMS Detect LVO?

Clinical Examination

Accuracy of Prediction Instruments for Diagnosing Large Vessel Occlusion in Individuals With Suspected Stroke: A Systematic Review for the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

Eric E. Smith, David M. Kent, Ketan R. Bulsara, Lester Y. Leung, Judith H. Lichtman, Mathew J. Reeves, Amytis Towfighi, William N. Whiteley, and Darin B. Zahuranec
and on behalf of the American Heart Association Stroke Council

Originally published 24 Jan 2018 | https://doi.org/10.1161/STR.0000000000000160 | Stroke. 2018;49:e111–e122

Multiple scales: RACE, LAMS, FAST-ED, BE FAST, etc.

No scale predicted LVO with both high sensitivity and high specificity. Systems that use LVO prediction instruments for triage will miss some patients with LVO and milder stroke.

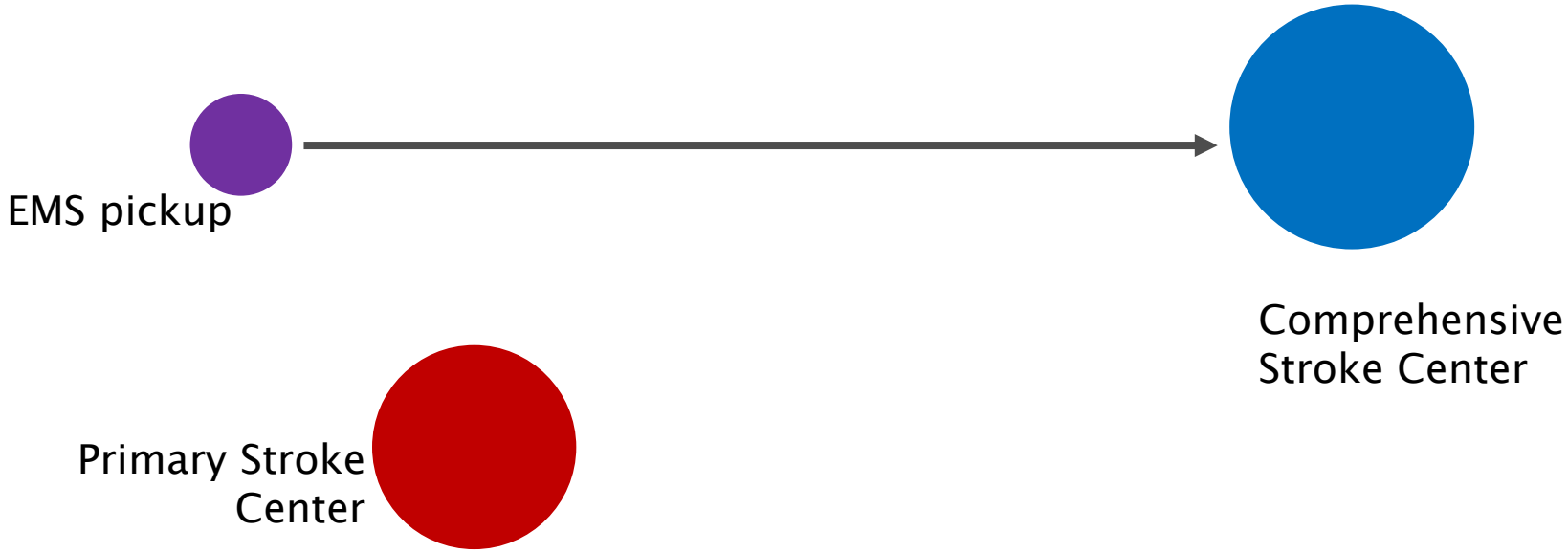
Ambulance-based "EKG" of the Brain

- EEG
- SSEP
- TCD
- Near Infrared Spectroscopy
- Microwave
- Accelerometry
- Volumetric Phase Shift Spectroscopy

(These are really "hemisphere dysfunction" detectors)

Smit EE, et al, Stroke, 2018
Patrick, L., et al. Current Emergency and Hospital Medicine Reports, 2021
Ramos, A., et al, Neurology, 2021

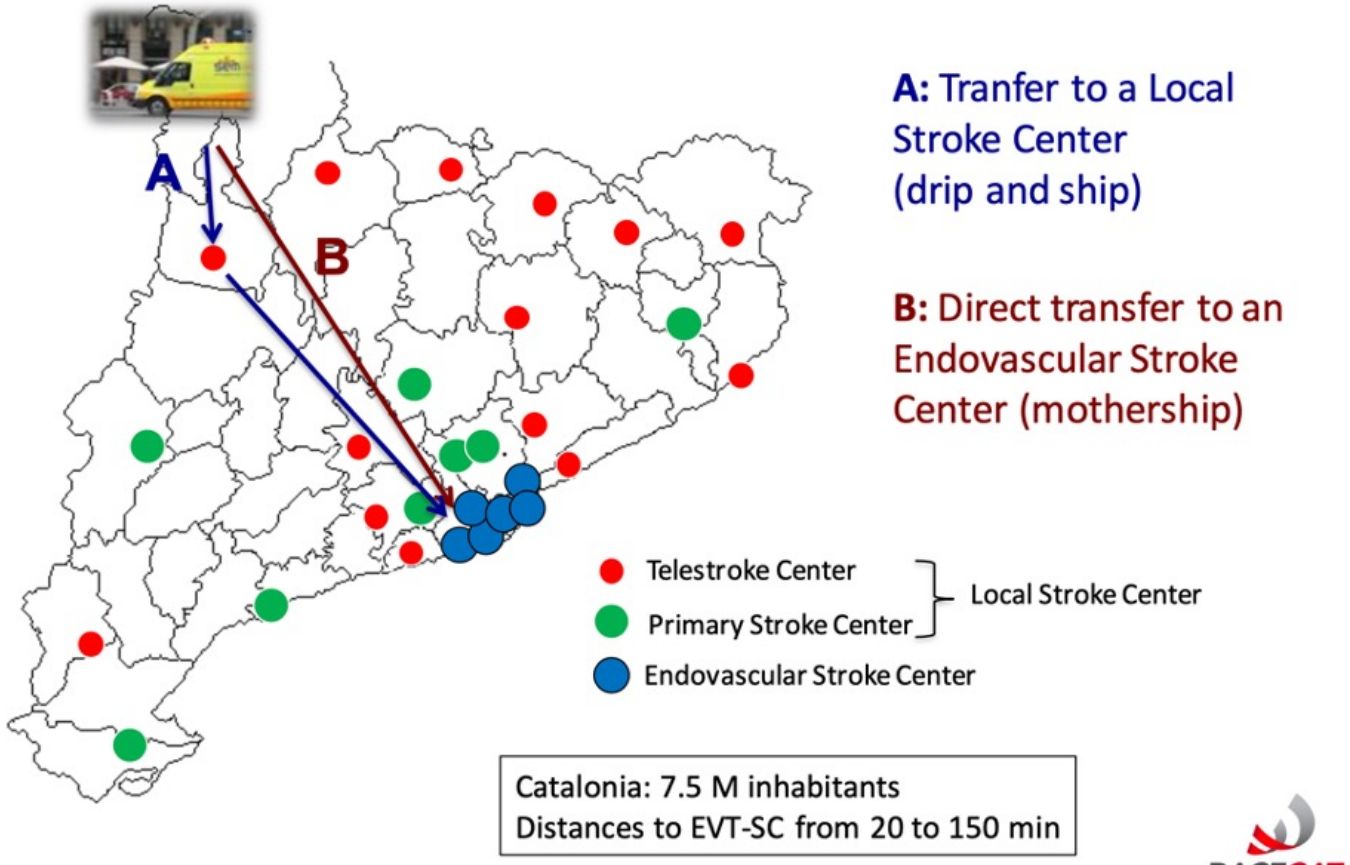
If LVO: Go Straight to the CSC



Mohamad et al, ESJ, 2016
Jayaraman et al, JNIS 2016
Parikh NS, et al, Stroke 2018

Should Suspected LVOs Bypass PSCs?

RACECAT Trial



Patients with a stroke and suspected LVO (RACE ≥5), located in geographical areas not covered by a CSC, and estimated arrival at an CSC within 7 hours of onset

1401 patients in final sample (PSC: 713, CSC: 688)

Trial was negative for the primary efficacy endpoint; a mothership transfer protocol in patients with suspected ELVO did not prove superior to the drip and ship protocol.

Perez de la Ossa et al, JAMA 2022

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Bypass for Suspected LVO

Unique population level data for suspected LVO

How did RACE perform?

Based on field assessment as-randomized:

Stroke: 920/1369= 67.2%

TIA: 29/1369= 1.6%

ICH: 314/1369= 22.9%

Mimics: 106/1369= 7.7%

LVO: 636/949= 67% (ITT)

=46.6% (as randomized)

RACE 7 (6-8) Median (IQR)

NIHSS 16 (9-21) median (IQR)

Participant Characteristics and Workflow Measures

Characteristics	Target population[b]	
	Thrombectomy-capable center (n = 482)	Local stroke center (n = 467)
Time from stroke onset to first hospital arrival, median (IQR), min	142 (100-231)	88 (61-145)
Time from stroke onset to first hospital arrival <4 h, No. (%)	370 (76.8)	403 (86.3)
Transferred to thrombectomy-capable center, No. (%)		302 (64.6)
Time from arrival to discharge at referral hospital (calculated in patients transferred), median (IQR), min		78 (63-97)
Time from arrival at first hospital to intravenous alteplase administration, median (IQR), min	30 (22-40)	33 (25-48)
Time from thrombectomy-capable center arrival to groin puncture, median (IQR), min	71 (49-97)	43 (32-59)

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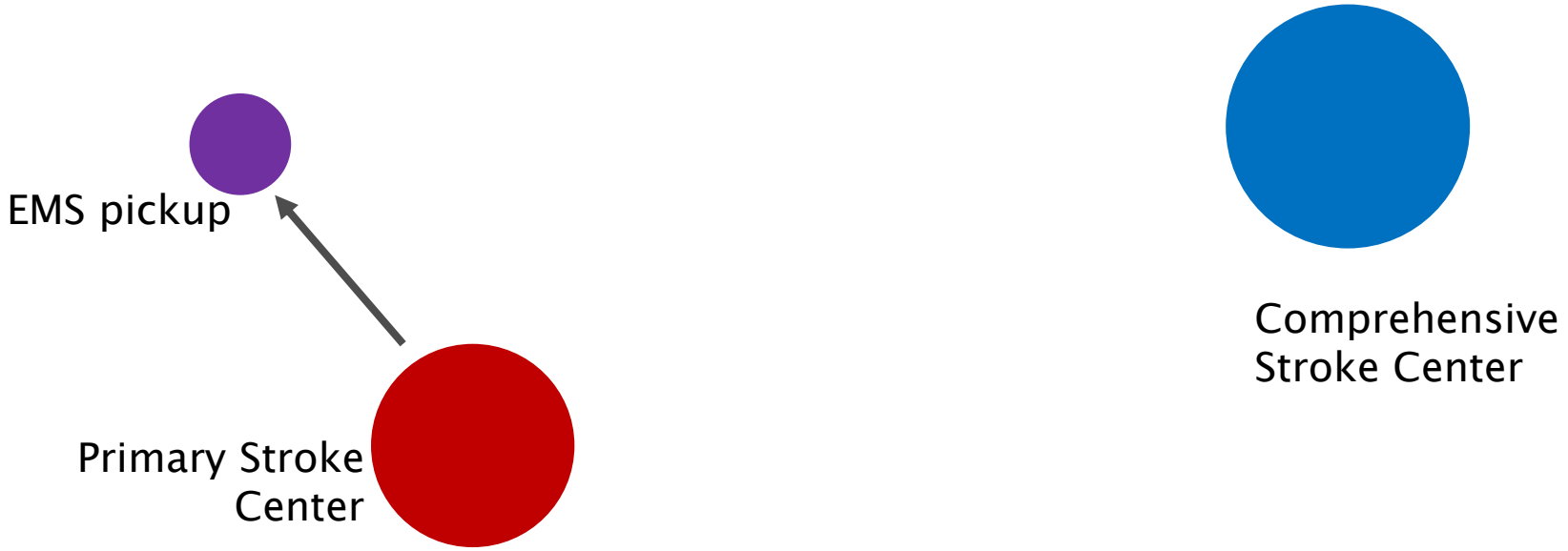
Perez de la Ossa et al, JAMA 2022

If LVO: Bring the PSC to the Patient



Mohamad et al, ESJ, 2016
Jayaraman et al, JNIS 2016
Parikh NS, et al, Stroke 2018

Can We Bring the Hospital to the Patient?

Mobile Stroke Units (MSU)

The Studied Model
"Double dispatch"
MSU + regular ambulance

CT scanner, POC labs, critical care nurse, vascular neurologist

IV alteplase on board

Goal: Faster thrombolysis

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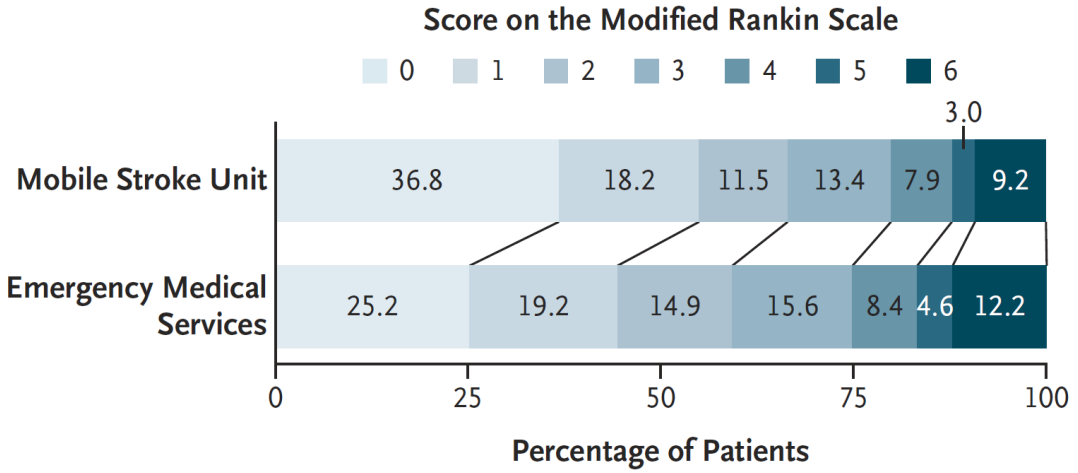
Mobile Stroke Units Impact Outcomes

BEST-MSU trial

Total 1047 patients (617 in the MSU group, 430 in the EMS group) were eligible for t-PA and were the population for primary analysis

Table 3. Time Metrics in Patients Eligible for t-PA.*

Interval	Mobile Stroke Unit	Emergency Medical Services
	minutes	
Median interval between the time that the patient was last known to be well and t-PA treatment (IQR)	72 (55–105)	108 (84–147)
Median time from 911 alert to t-PA treatment (IQR)	46 (39–55)	78 (66–93)
Median time from ED door to t-PA bolus (IQR)	—	40 (30–51)
Median interval between the time that the patient was last known to be well and the alerting of emergency medical services (IQR)	23 (8–52)	22 (11–60)
Median time from 911 alert to arrival of emergency medical services (IQR)	9 (6–13)	9 (6–13)
Median time from arrival of emergency medical services to ED arrival (IQR)	55 (47–62)	27 (21–33)
Median interval between the time that the patient was last known to be well and endovascular thrombectomy (IQR)	166 (131–202)	163 (134–209)
Median time from 911 alert to endovascular thrombectomy (IQR)	141 (116–171)	132 (114–160)
Median time from ED door to endovascular thrombectomy (IQR)	76 (53–105)	94 (72–124)



The mean score on the utility-weighted mRS at 90 days in patients eligible for t-PA was 0.72 in the MSU group and 0.66 in the EMS group (adjusted odds ratio for a score of ≥0.91, 2.43; 95% confidence interval [CI], 1.75 to 3.36; P<0.001).

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Grotta JC, et al, NEJM 2021

What do Mobile Stroke Units Offer LVO?

New rigs are equipped with CTA capability for LVO detection

Table 2. Time Metrics Between MSU CT and MSU CT/CTA Groups

	MSU CT (n=84)	MSU CT/CTA (n=20)	*P* Value
DTPT, min, median (IQR)	94.5 (69.8–117.3)	41.0 (30.0–63.5)	<0.001
MSU on-scene time, min, median (IQR)	27.0 (23.0–31.0)	31.5 (28.8–35.5)	<0.001
Alert to ED arrival time, min, median (IQR)	63.5 (53.0–72.3)	68.5 (59.3–79.0)	0.12

CT indicates computed tomography; CTA, computed tomography angiography; DTPT, door-to-puncture time; ED, emergency department; IQR, interquartile range; and MSU, mobile stroke unit.

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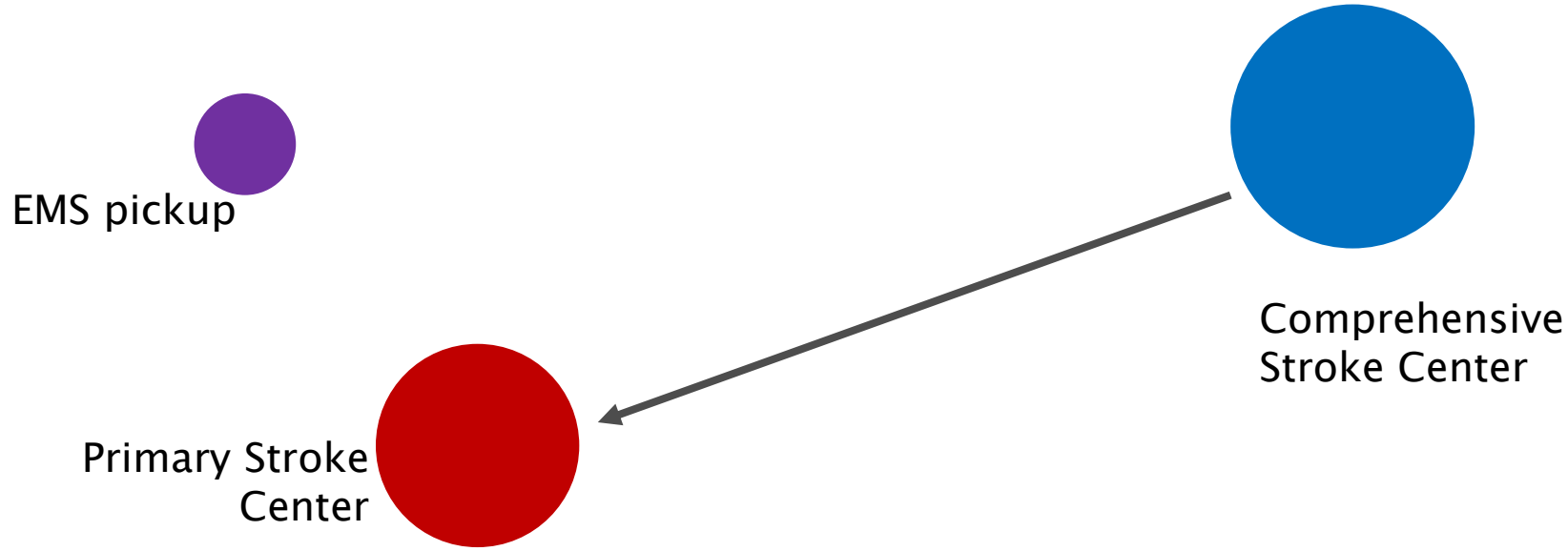
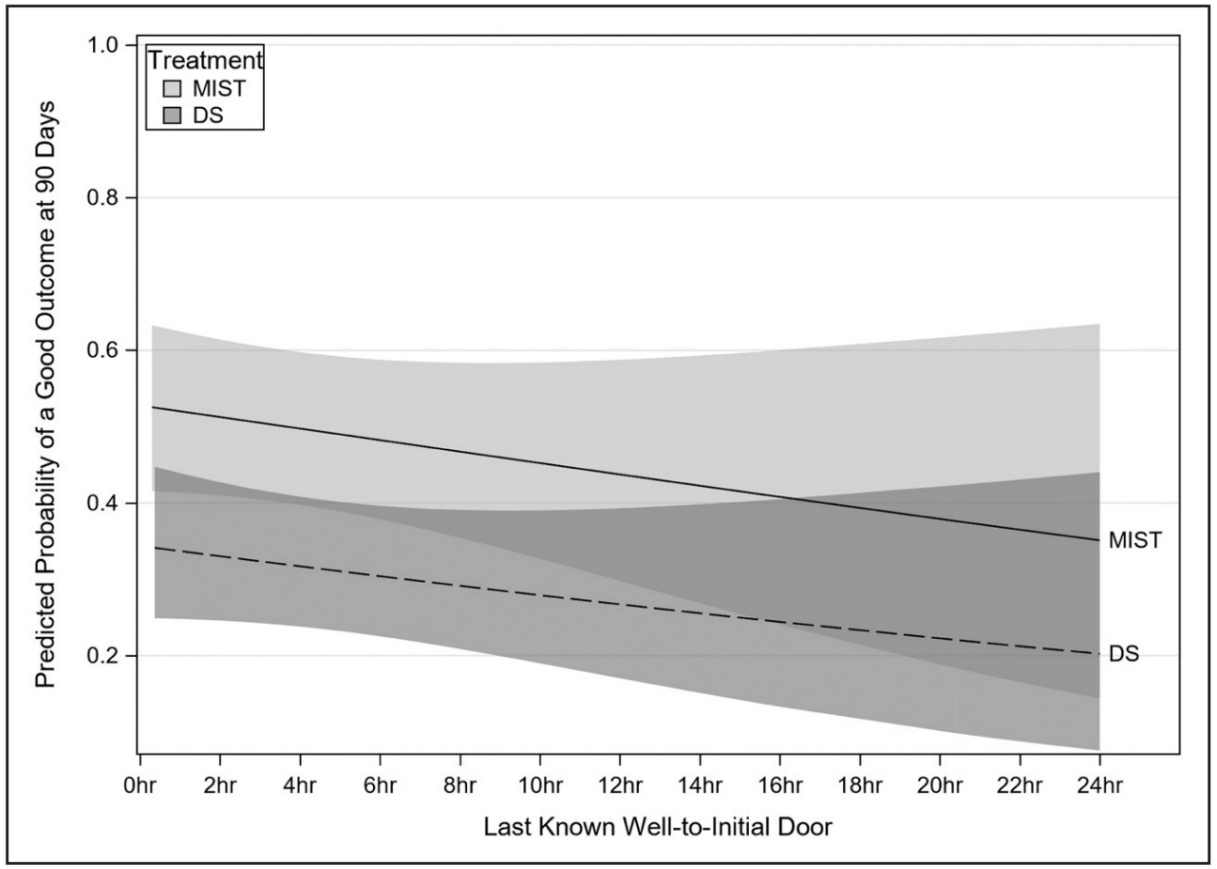
Czap AL, et al. Stroke. 2020

If LVO: Bring the CSC to the PSC



Mohamad et al, ESJ, 2016
Jayaraman et al, JNIS 2016
Parikh NS, et al, Stroke 2018

What About Moving the Team Instead?



Probability of a good outcome by Last Known Well to Initial Door time interval.

MIST

New York City Subway

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Morey, et al, Stroke 2021

What About Moving the Team Instead?

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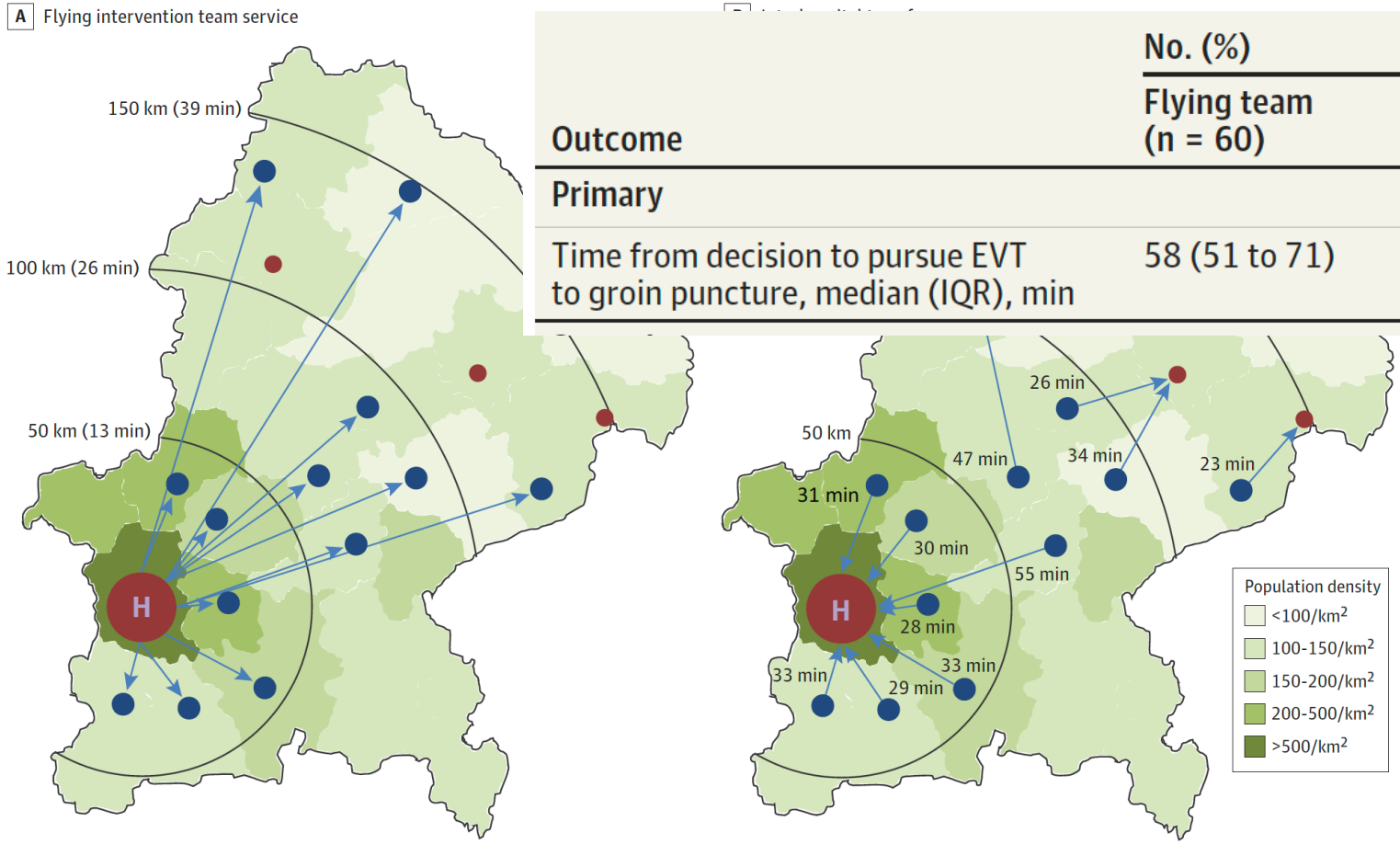
What About Moving the Team Instead?

TEMPIS



Outcome	No. (%) Flying team (n = 60)	Transfer (n = 57)	Absolute difference (95% CI)	*P* value[a]
Primary				
Time from decision to pursue EVT to groin puncture, median (IQR), min	58 (51 to 71)	148 (124 to 177)	90 (75 to 103)	<.001

Fast times but no significant difference in 90-day mRS between patients in the flying team and transfer groups who received EVT.

Trial was underpowered for clinical outcome

SE Bavaria TEMPIS network

Hubert, JAMA 2022

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What Might This Mean for Our LVO Patients?

Robust systems of care produce robust outcomes

- There is no clear bypass advantage for LVO patients in such systems
- But are our systems currently robust?
- Where should our energy be spent?

Mobile stroke units are likely to proliferate

- What protocols and staffing considerations are needed, and will on-board capability expand?
- How will funding models change?

Action to shorten the time between a patient and treatment expertise will impact outcome positively

- Mobilizing a Neuroendo team is an effective approach to save time
- But at what cost?

THROMBOLYTICS

tPA Before Thrombectomy

Give alteplase
Enhanced success of thrombectomy
Prevention of microvascular thrombosis
Recanalization without the need for mechanical thrombectomy
Recanalization for those patients unable to undergo mechanical thrombectomy or with treatment delay

Leslie-Mazwi TM et al, AJNR 2017

Should We Defer IV tPA for LVO Patients?

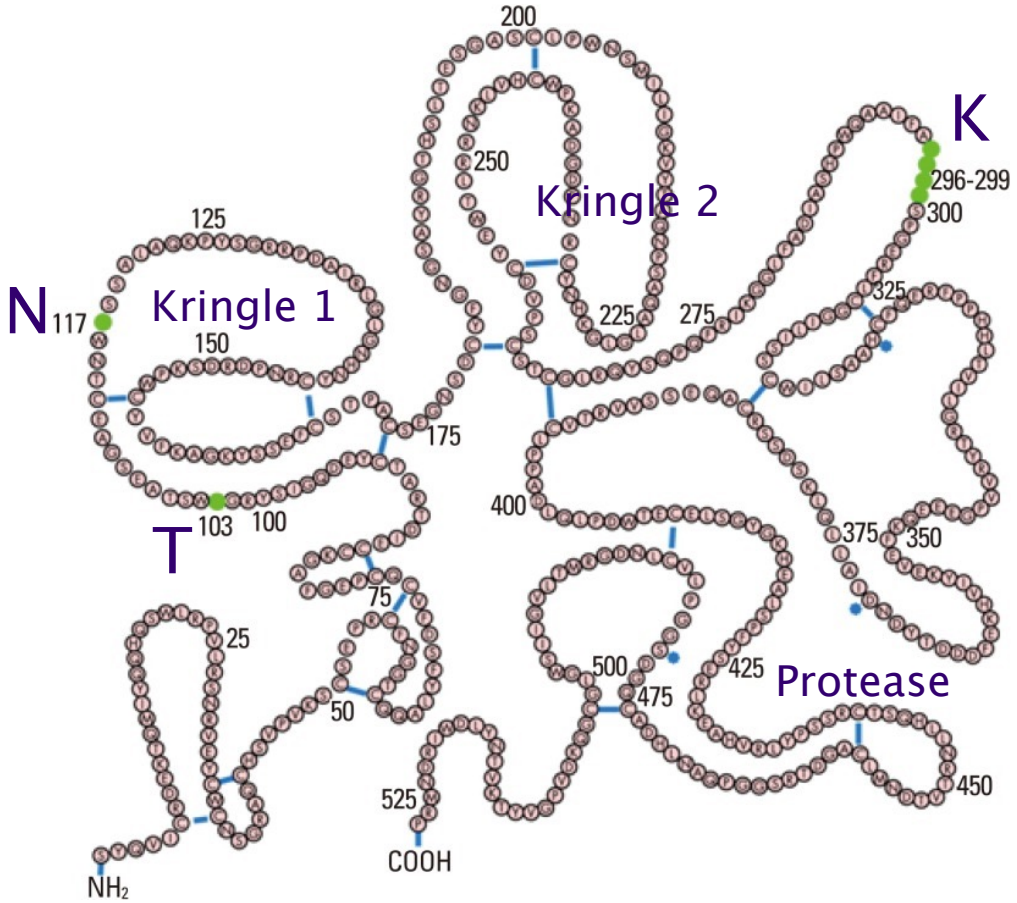
SKIP
DEVT
DIRECT-MT
MR CLEAN NO-IV
SWIFT-DIRECT
DIRECT-SAFE

"Thrombectomy alone may be considered in eligible patients with demonstrated LVO and immediate availability of thrombectomy where the pursuit of IV **alteplase** may delay puncture time"

→ Only a CSC controversy

Yang P, et al, NEJM 2020
Zi W, et al, JAMA 2021
Suzuki K, et al, JAMA 2021
LeCouffe NE, et al, NEJM 2021

Tenecteplase



Tenecteplase molecule

Properties vs. alteplase

15x greater fibrin specificity

6x longer half life

80x resistance to PAI-1

The Food and Drug Administration has approved IV tenecteplase for the treatment of acute myocardial infarction, and it is the commonly used thrombolytic when PCI is not immediately available.

Huang X, et al, Lancet Neurol 2015 (ATTEST)
Logallo N, et al, Lancet Neurol 2017 (NOR-TEST)

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Trials Evaluating Tenecteplase in Stroke

Within 4.5hrs of onset

ATTEST 2 (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis)

NOR TEST 2 (The Norwegian Tenecteplase Stroke Trial 2)

In LVO Patients

BRETIS-TNK (Boosting REcanalization of Thrombectomy for Ischemic Stroke by Intra-arterial TNK)

TASTE (Tenecteplase vs Alteplase for Stroke Thrombolysis Evaluation)

TEMPO 2 (TNK– Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion)

Late Window/Unwitnessed Onset

CHABLIS-T (Chinese Acute Tissue-Based Imaging Selection for Lysis In Stroke-Tenecteplase)

ETERNAL-LVO (Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel Occlusion)

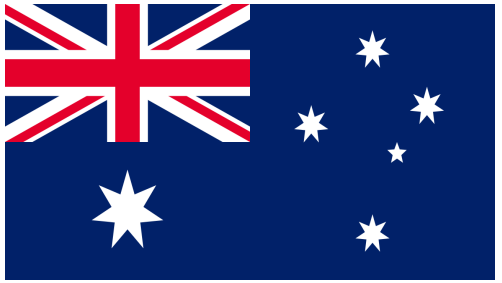
ROSE-TNK (MRI-guided thrombolysis for Stroke bEyond Time Window by TNK)

TIMELESS (Thrombolysis in Imaging-Eligible, Late-Window Patients to Assess the Efficacy and Safety of Tenecteplase)

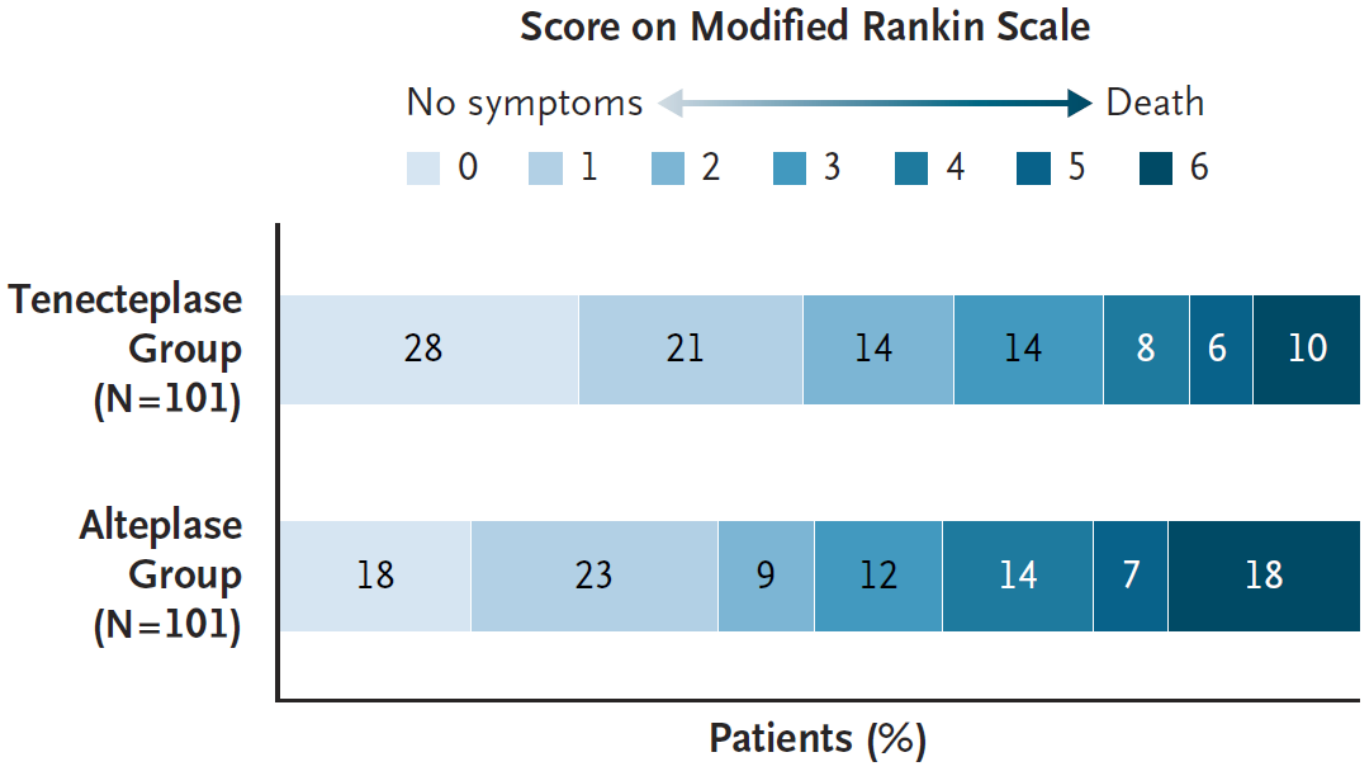
TWIST (Tenecteplase in Wake-Up Ischaemic Stroke Trial)

Dong Y, et al. Stroke & Vascular Neurology 2022

Tenecteplase for LVO Patients



EXTEND-IA TNK 1+2



Tenecteplase dose 0.25mg/kg to 25mg max, LVO patients randomized pre-thrombectomy

Tenecteplase resulted in a higher incidence of reperfusion of the occluded vascular territory before endovascular thrombectomy than did intravenous alteplase: 22% vs 10%

Patients in the tenecteplase group had a median mRS of 2, as compared with a median mRS of 3 among patients in the alteplase group (common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P = 0.04).

Campbell B, et al, NEJM 2018
Campbell B, et al, NEJM 2020
Alemseged F, et al, Neurology 2021

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Should We Move to Tenecteplase?

What is the bar Tenecteplase must surmount?

Is This Finally The Straw …?

AcT Trial

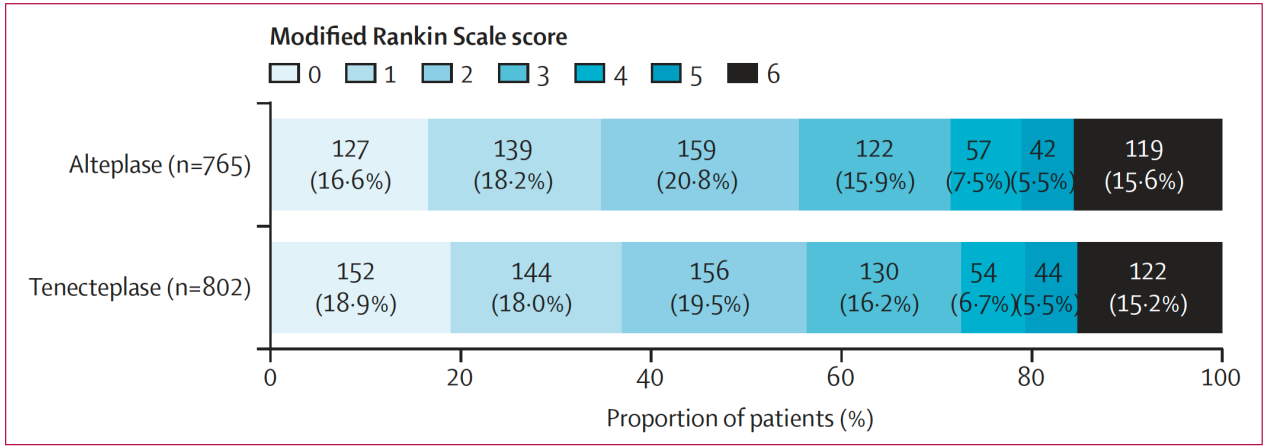

Figure 2: **Distribution of the modified Rankin Scale scores at 90–120 days, intention-to-treat population**
Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

1600 patients were enrolled and randomly assigned to tenecteplase (n=816) or alteplase (n=784). Tenecteplase dosing was 0·25 mg/kg.

mRS score of 0–1 at 90–120 days (unadjusted risk difference 2·1% [95% CI – 2·6 to 6·9] between groups met the prespecified non-inferiority threshold. Similar rates of complications.

"Given the ease of use of tenecteplase versus alteplase, results from the AcT trial, when combined with evidence to date, provide a compelling rationale to switch the global standard for thrombolysis to tenecteplase at a dose of 0·25 mg/kg in patients with acute ischaemic stroke who present within 4·5 h of symptom onset."

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Menon, et al, Lancet 2022

What Might This Mean For Our LVO Patients?

If we make a wholesale switch to Tenecteplase instead of Alteplase:

What are the implications for LVO patients and bypass? Telestroke? Direct-to-angio protocols?

What are the implications for MSUs and LVO patients?

Do we need to study the effect of skipping Tenecteplase for LVO patients?

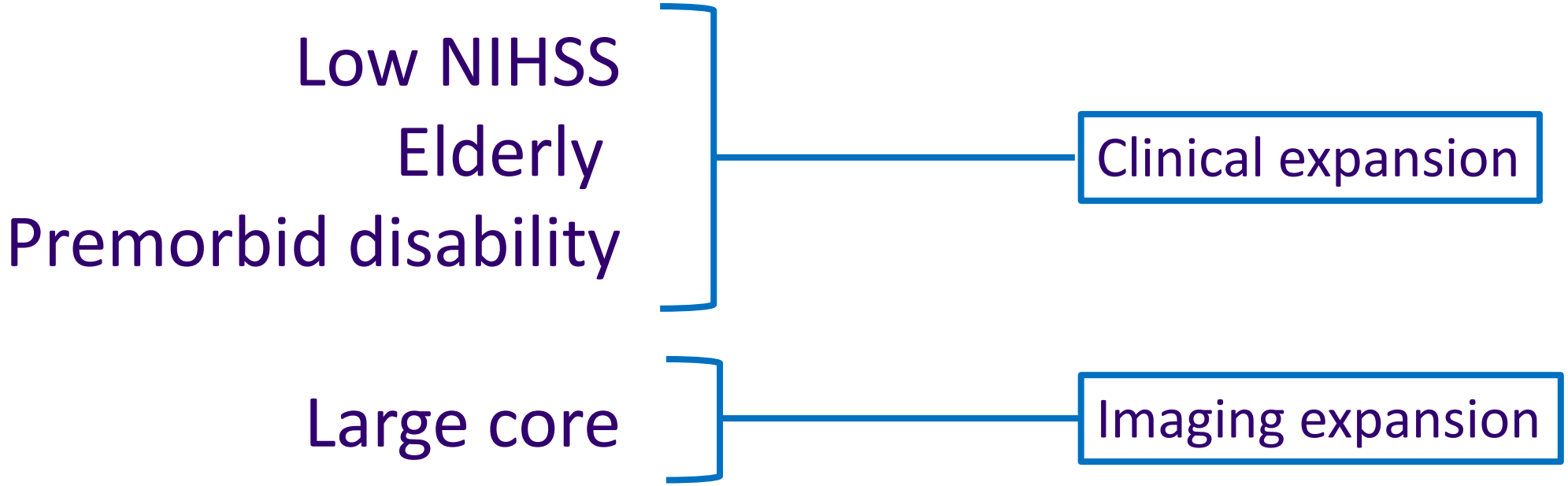
(DIRECT-TNK is enrolling: NCT05199194)

THROMBECTOMY

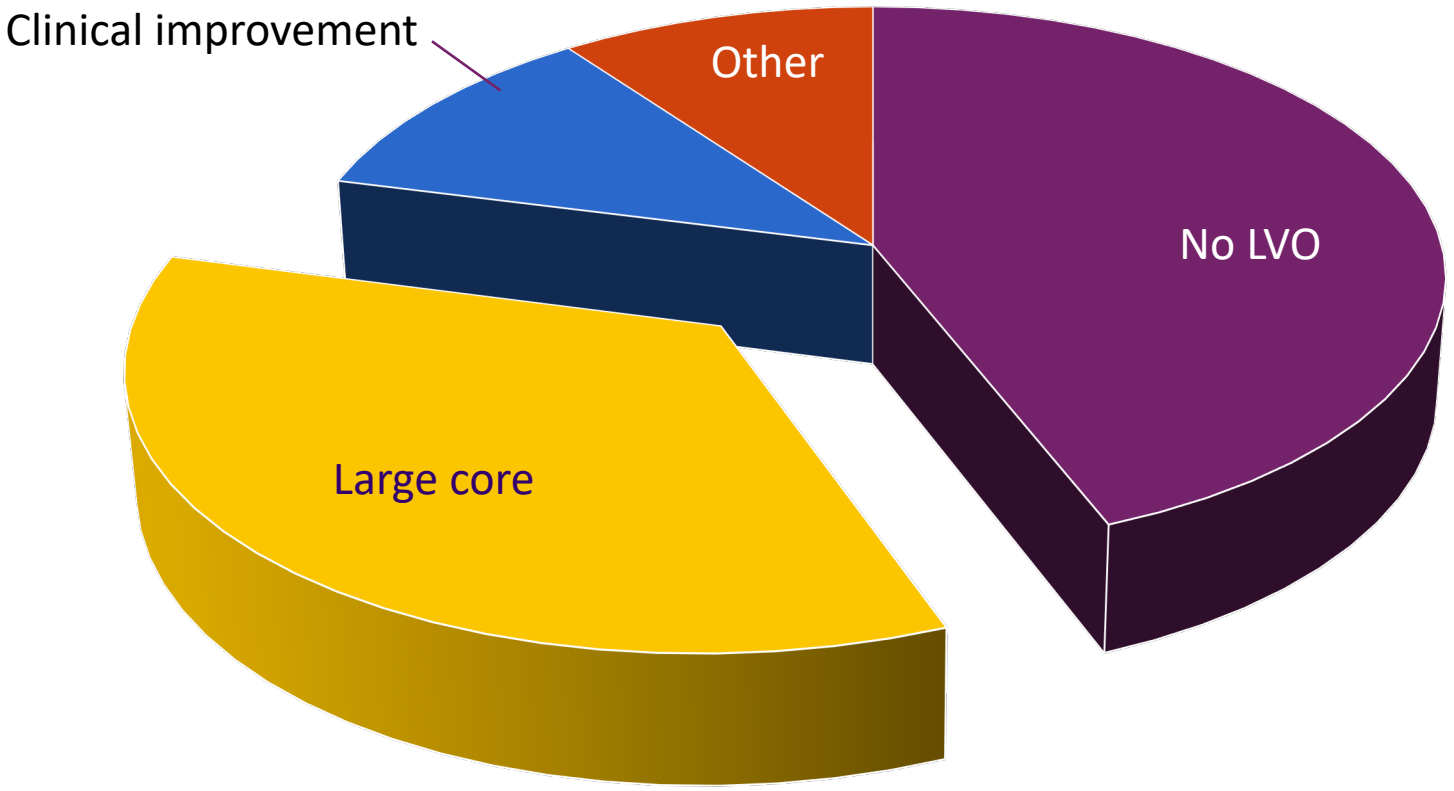
Selection

Patient Selection for Thrombectomy

The magnitude of benefit for LVO patients treated with thrombectomy is among the largest observed in medicine. **Let's not be stingy…**



A Large Ischemic Core is a Common Exclusion



Transferred patients with suspected LVO who were ineligible for thrombectomy

Leslie-Mazwi, et al, JAMA Neurol, 2016

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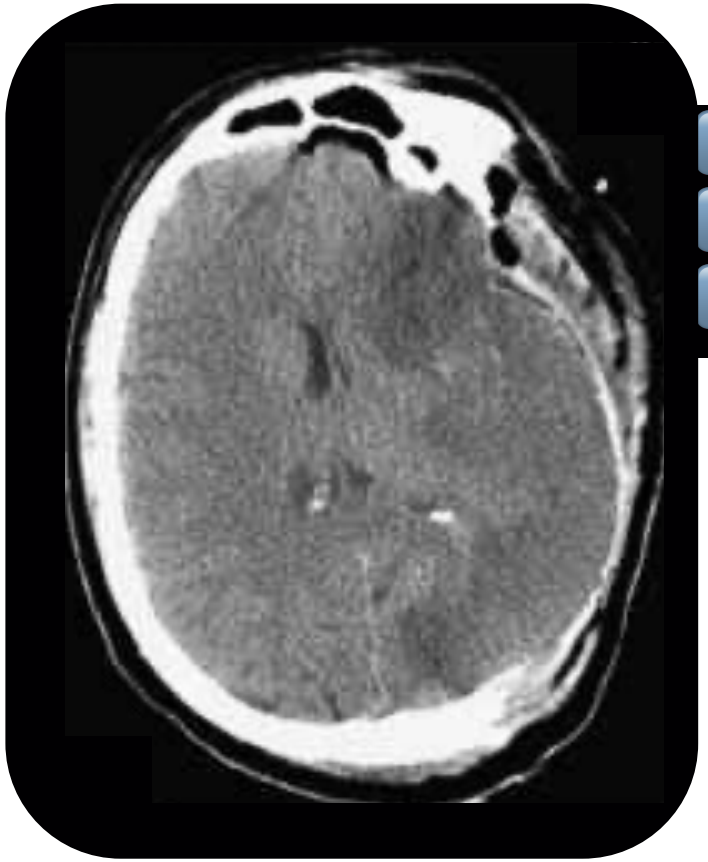
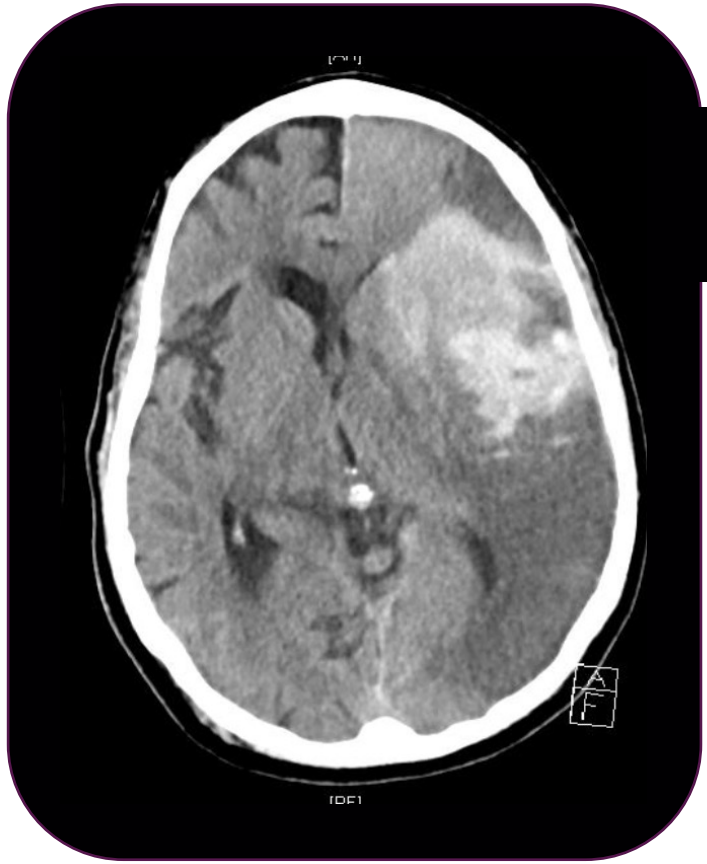
Data is Mixed for Large Core Patients



- Hemicraniectomy
- Mortality
- Recovery

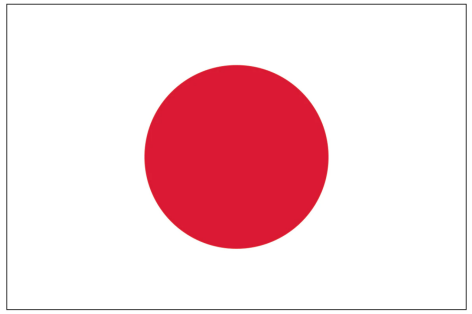
Sarraj A, et al, JAMA Neurol 2019
Rebello et al, JAMA Neurol 2017
Tisserand, et al, Stroke 2016
Gilgen, et al, Stroke 2015



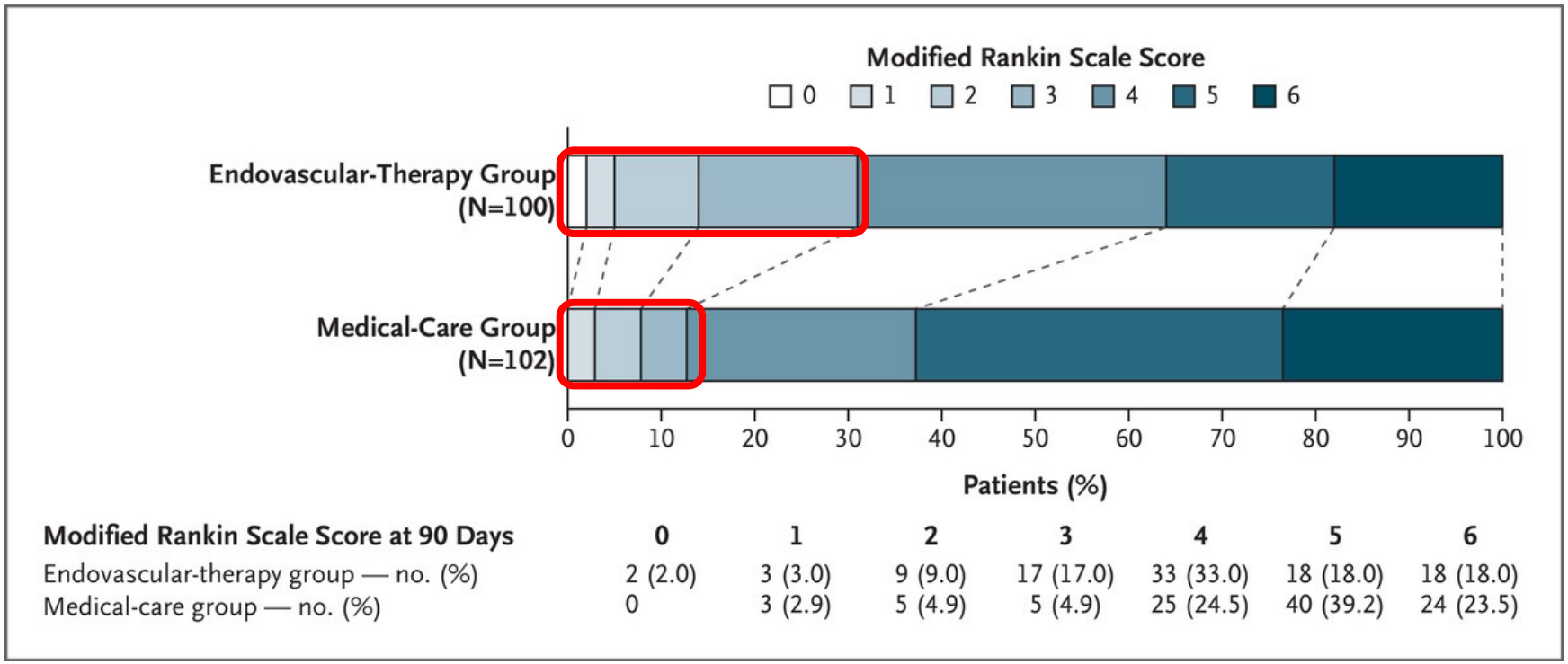
- Hemorrhage
- Value

Meyer L, et al, Stroke 2021
Mlynash, et al, Stroke 2011
Kidwell et al, NEJM 2013
Yoo, et al, Stroke 2009

Large Core Patients Do Benefit



RESCUE-Japan trial



Modified Rankin Scale Score at 90 Days	0	1	2	3	4	5	6
Endovascular-therapy group — no. (%)	2 (2.0)	3 (3.0)	9 (9.0)	17 (17.0)	33 (33.0)	18 (18.0)	18 (18.0)
Medical-care group — no. (%)	0	3 (2.9)	5 (4.9)	5 (4.9)	25 (24.5)	40 (39.2)	24 (23.5)

Distribution of Modified Rankin Scale Scores at 90 Days.

45 Japanese Hospitals
86% selected with MRI
ASPECTS 3-5
28% given alteplase (0.6mg/kg)

mRS 0-3 was 31.0% in the endovascular-therapy group vs. 12.7% in the medical-care group (relative risk, 2.43; 95% confidence interval [CI], 1.35 to 4.37; P=0.002)
No significant between-group difference in sICH or mortality at 90 days (though more ICH in endo group)

Yoshimura S, et al. N Engl J Med 2022

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But We Cannot Celebrate Too Soon…

There are important caveats for RESCUE Japan:

Alteplase dosing was 0.6mg/kg, and infrequent

Patients were predominantly early (<6hrs), so rapid progressors

MRI was predominantly used for selection

Good outcome was considered mRS 0-3

Other Trials are Still Pending

TENSION

NCT03094715
LSW <11hrs, ASPECTS 3-5 on NCCT or DWI

IN EXTREMIS LASTE

NCT03811769
LSW <6.5hrs, ASPECTS 0-5 on NCCT or DWI

SELECT2

NCT03876457
LSW <6.5hrs, ASPECTS 3-5 or core >50cc on NCCT or DWI

TESLA

NCT03805308
LSW <24hrs, ASPECTS 2-5 on NCCT or DWI

What Might This Mean For Our LVO Patients?

Regarding thrombectomy for large core patients:

There is still equipoise, trial enrollment should continue

- Data will likely need to be combined for the most complete picture

Value and cost analyses will be important

- Societal versus patient benefit

We can be more liberal pushing for thrombectomy in large core patients in certain subgroups

- “Let the dust settle”

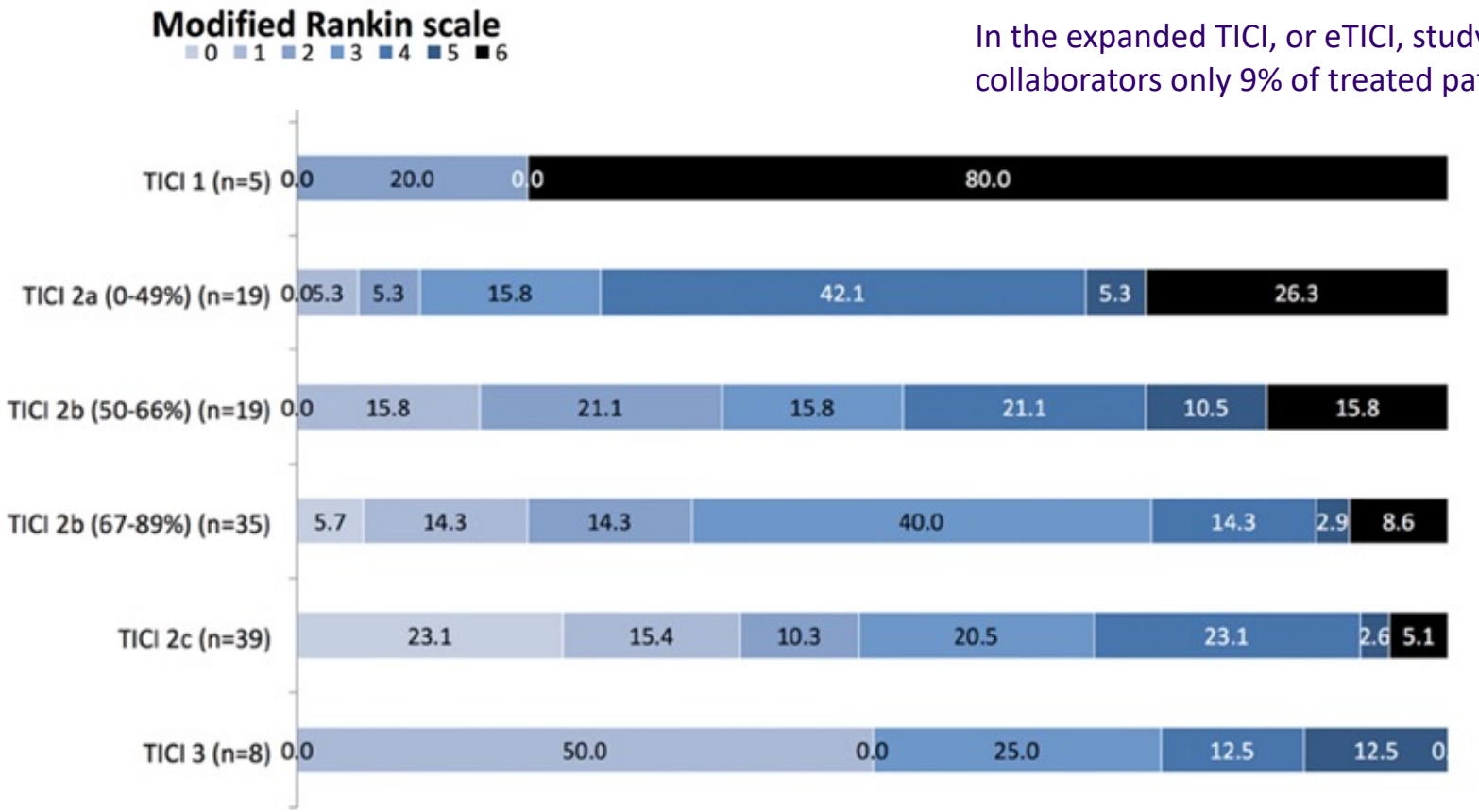
THROMBECTOMY

Reperfusion

Reperfusion: More is Better

Distal occlusions limit reperfusion

In the expanded TICI, or eTICI, study from the HERMES collaborators only 9% of treated patients achieved TICI 3



Increasing reperfusion

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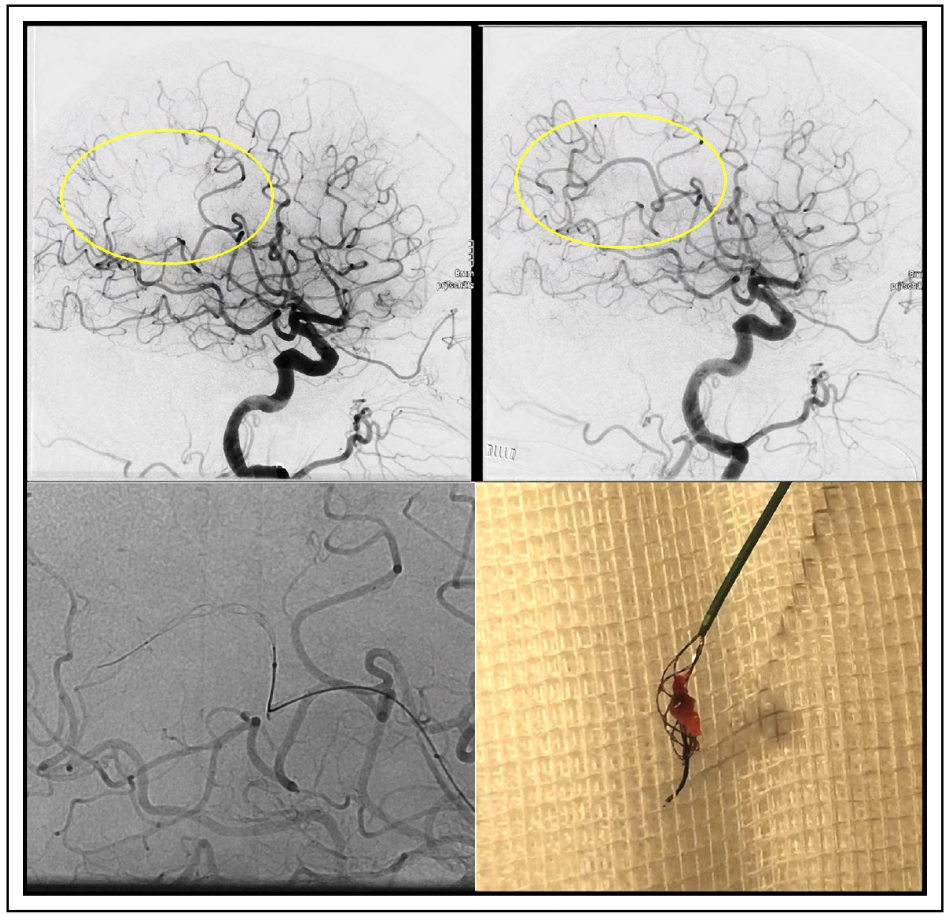
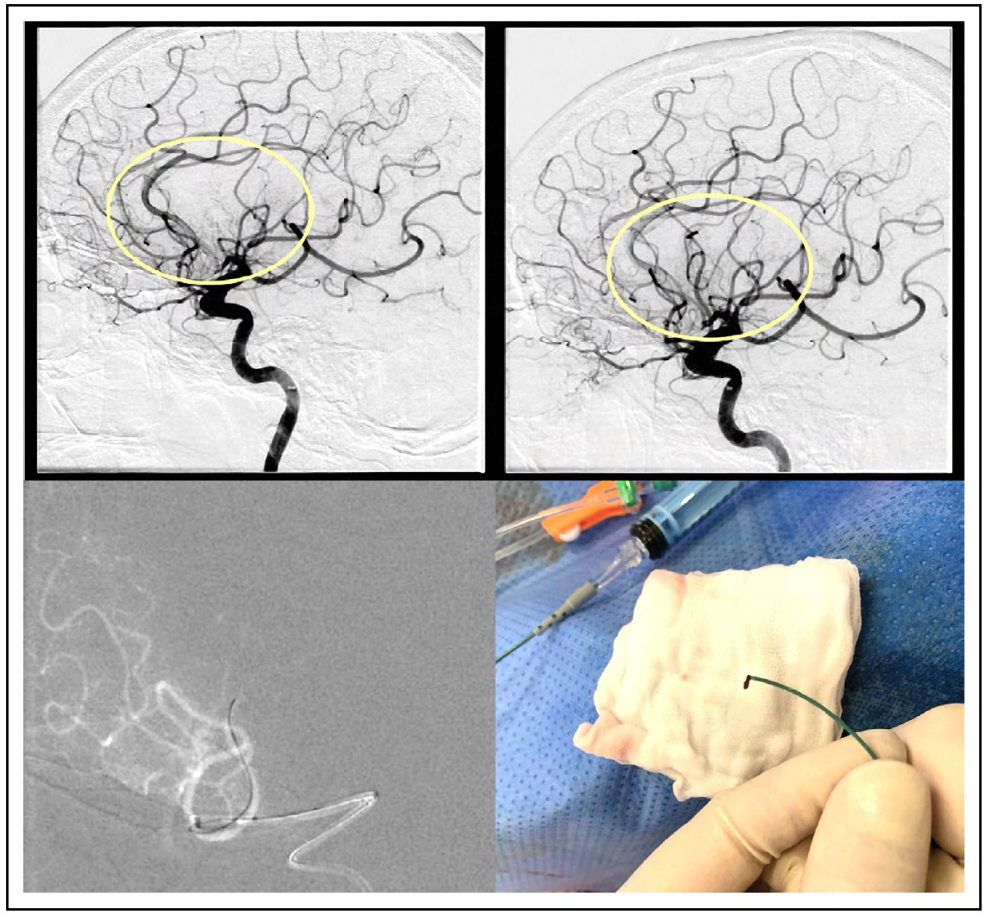
Liebeskind DS, et al. JNIS 2019

Distal Mechanical Thrombectomy

Minimization is a feature of technological advancement

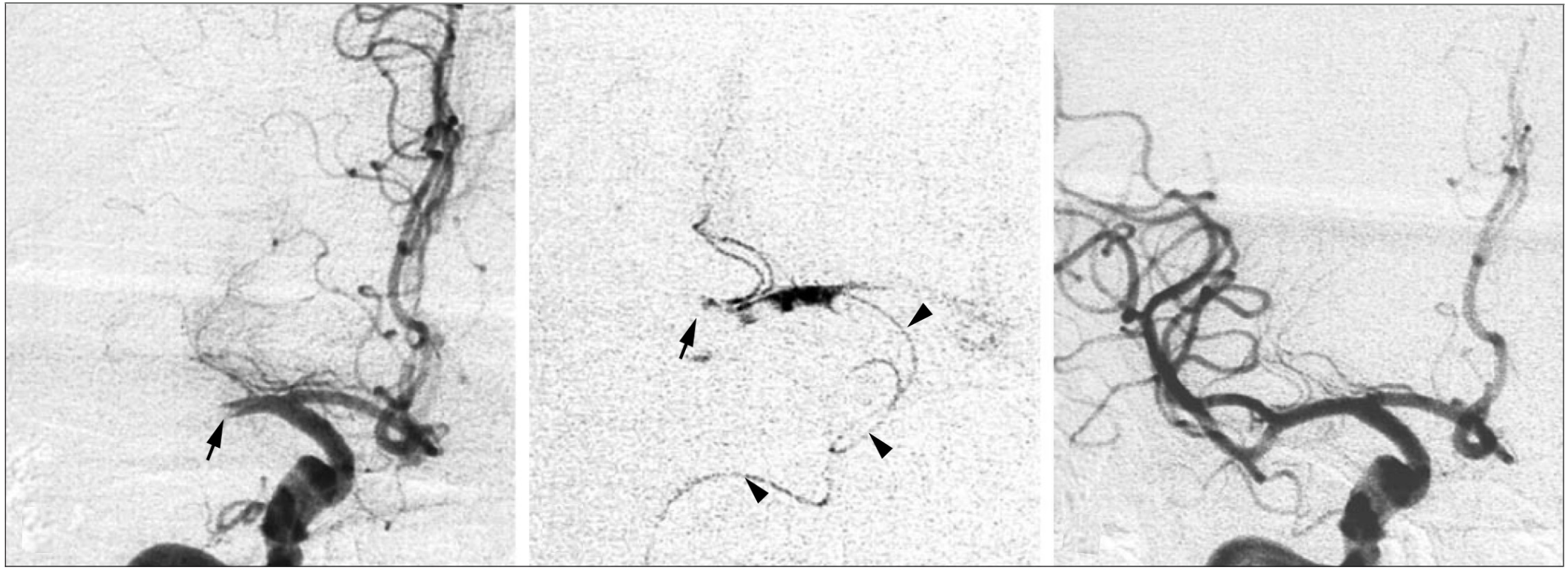




Is the Past Prologue?

PROACT II (Prolyse in Acute Cerebral Thromboembolism II)

1996–1998, 180 patients, 54 centers in the USA and Canada, treatment initiation <6hrs



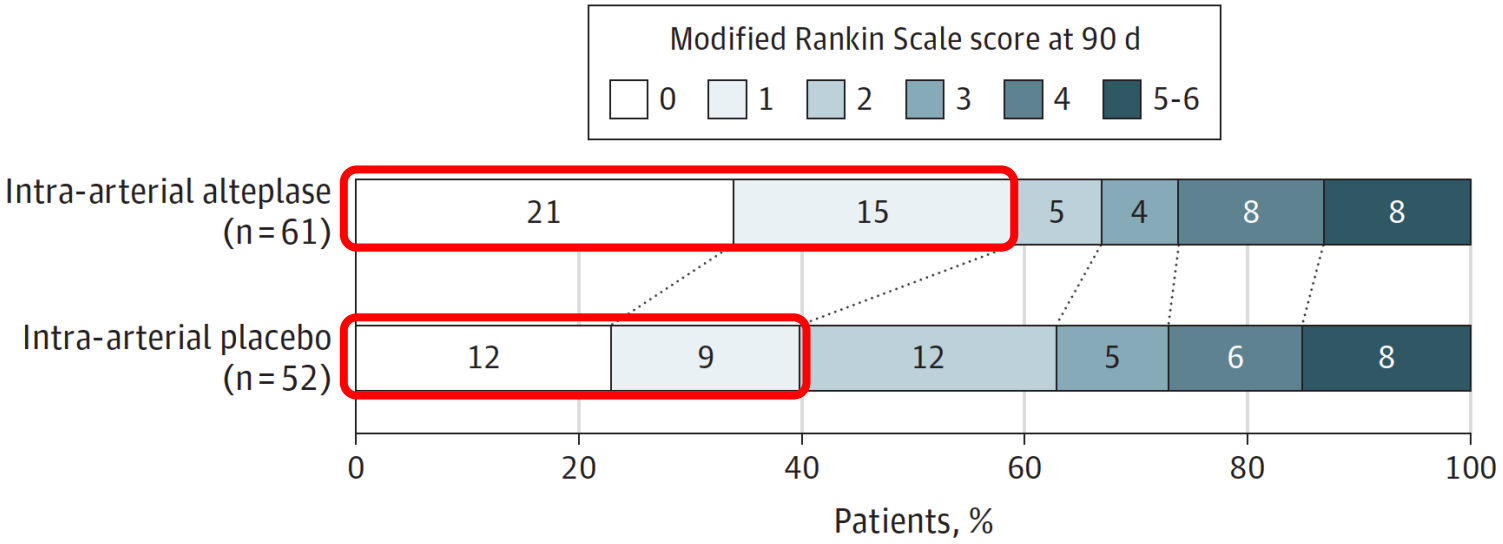
Initial | 1 hour | 2 hours

Furlan et al, JAMA 1999

Can We Achieve Greater Reperfusion?

CHOICE Trial

Does improving reperfusion of the microcirculation help?



7 Catalonian hospitals
Standard alteplase IV (though could be stopped prematurely by operator)
Patients randomized to intra-arterial alteplase received a dose of 0.225 mg/kg (maximum dose, 22.5 mg) infused over 15-30 minutes. Alteplase or placebo was injected distally to the origin of the lenticulostriate branches.
Excellent outcome in participants treated with IA alteplase compared with placebo (59.0% vs 40.4%; 95% CI, 0.3%-36.4%; P = .047).

Renu A, et al, JAMA 2022
Khatri P, JAMA 2022

UNIVERSITY of WASHINGTON

What Might This Mean For Our LVO Patients?

Achieving full, not just fast, reperfusion is increasingly our goal

- That will take more than just mechanical device evolution

Based on CHOICE consider IA lytic in cases with impaired distal flow after primary recanalization

- Alteplase was studied and has more IA experience
- Whether alteplase or tenecteplase offers better IA reperfusion is unknown

Expect more trials to explore this question

In Conclusion…

There are many questions to answer

Dynamic randomized trials are helping inform us better, from all across the world

We must be ready to bridge the Evidence-Practice Divide

New trial designs will accelerate this timeframe
(e.g. STEP platform trial- **S**trokeNet **T**hrombectomy **E**ndovascular **P**latform)

We are all so lucky to work in the cerebrovascular field at this time!

Thank you

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