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Treating Low NIHSS Strokes

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Treating Low NIHSS Strokes

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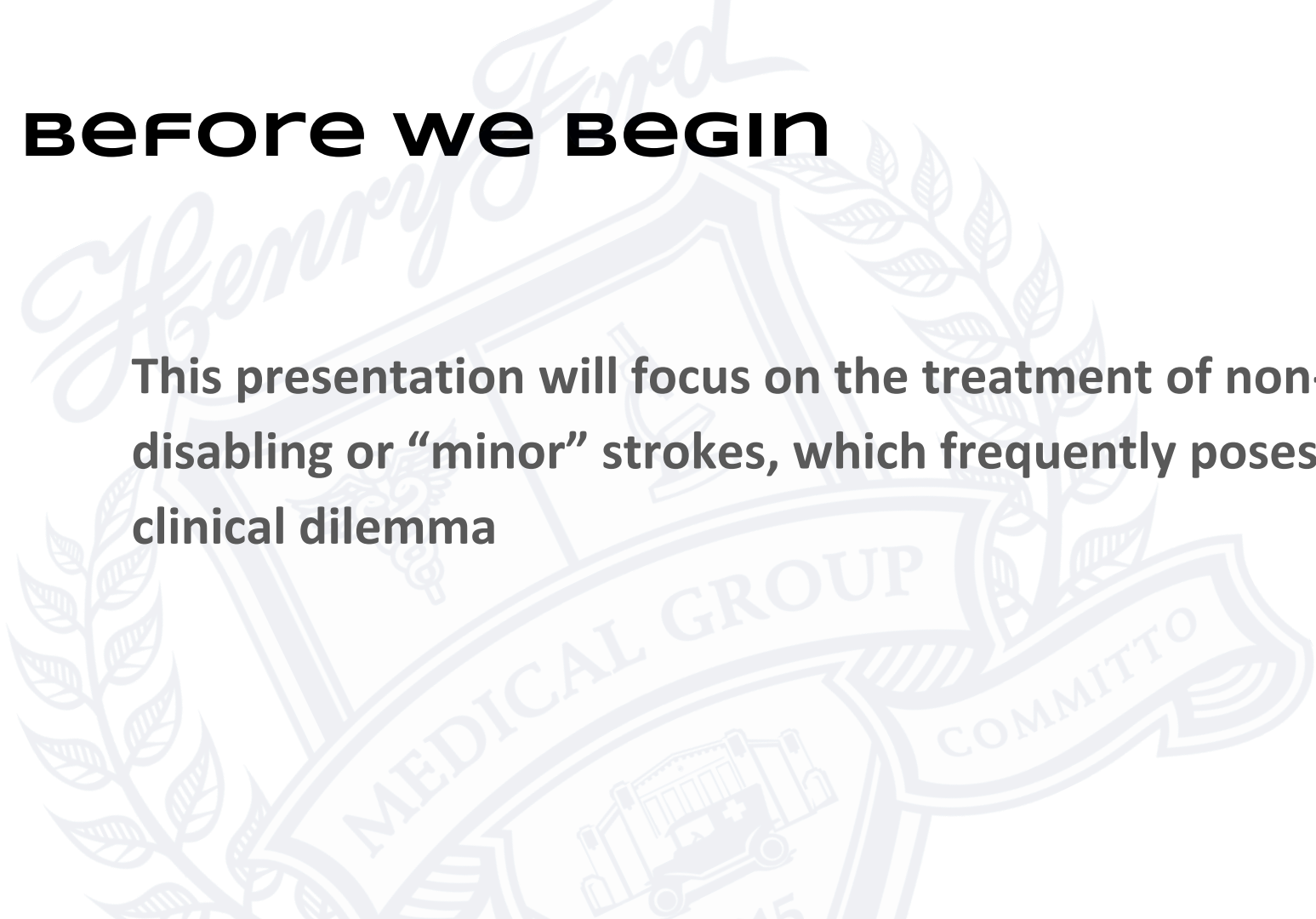
Department of Neurology

Henry Ford Hospital



BEFORE WE BEGIN

This presentation will focus on the treatment of non-disabling or “minor” strokes, which frequently poses a clinical dilemma



on THE menu

- Definition, prevalence and prognosis of low NIHSS strokes (LNS)
- How can we predict deterioration of minor strokes?
- Intravenous thrombolysis in LNS
- Mechanical thrombectomy in LNS
 - Proximal occlusions
 - Distal occlusions

DISABLING STROKES



minor strokes



WHY are LNS WORTH TALKING ABOUT?

- Any stroke type can present with minor symptoms initially
- Minor LVO strokes can quickly become severe and disabling
 - Expansion of clot
 - Complete vessel occlusion
 - Failure of collaterals
 - Hemodynamic compromise, reduction in oxygen carrying capacity of blood
- Many times, acute intervention is foregone because the thought is that risks outweigh benefits
- We need better patient selection and prediction tools to understand which patients will deteriorate and therefore needs emergent therapy

A UNIQUE AND CHALLENGING POPULATION

- **Difficult identification**
 - What is considered a LNS? <10? <6? <4?
 - NIHSS is imperfect
- **Difficult researchability**
 - Low prevalence and incidence
 - Slow enrollment
 - Heterogeneity in identification of LNS
- **Difficult predictability**
 - Unpredictable course, potential for worsening/deterioration
 - Particularly true for LVO

EPIDEMIOLOGY OF LNS

- Get With The Guidelines (GWTG)–Stroke registry ¹
 - 33,995 patients
 - 22.4% had an NIHSS score < 6
- Safe Implementation of Treatment in Stroke (SITS) registry ²
 - 24.9% of patients with NIHSS scores < 6 had a LVO
- In one study ³, of 29 patients who had LVO and a favorable penumbra but were not deemed eligible for MT, 5 (16%) were not considered because of mild symptoms

¹ Romano, et al. *JAMA Neurol.* 2015;72:423-431

² Mazyra, et al. *Eur Stroke J.* 2018;3:29-38

³ Hosseini, et al. *J Neuroimaging.* 2018 Nov;28(6):676-682

CHALLENGING POPULATION TO research

- We don't have the numbers!
 - For mechanical thrombectomy
 - No available RCT on LNS with LVO
 - Of the 5 landmark MT trials, only MR CLEAN included patients with NIHSS <6
 - For IV thrombolysis
 - The main RCT available, PRISMS, was underpowered and stopped enrolling prematurely
- Wide variability in definition of low NIHSS across studies
 - NIHSS threshold anywhere between 3 and 10
 - Variable distribution of occlusion sites in LVO cases across studies

NATURAL COURSE OF LNS

- **Presence of a symptomatic arterial occlusion** is strongest independent predictor of early neurologic deterioration
 - In one study ¹, untreated LVO were 2x more likely to expand stroke (OR= 2.206; 95% CI, 1.219–3.994; *P* = .009)
 - In another study ², untreated **proximal** LVO (M1/ICA) were 7x more likely to have poor outcome (OR= 7.13; 95% CI, 1.1–45.5; *P* < .038)
- Unfavorable prognosis of untreated LNS with LVO
 - In one study ³, 22.7% of patients deteriorated within 24 hours, 33.3% during hospital stay, and 41.4% within 3 months. Mortality rate = 6.7%.
 - Stats echoed in other studies

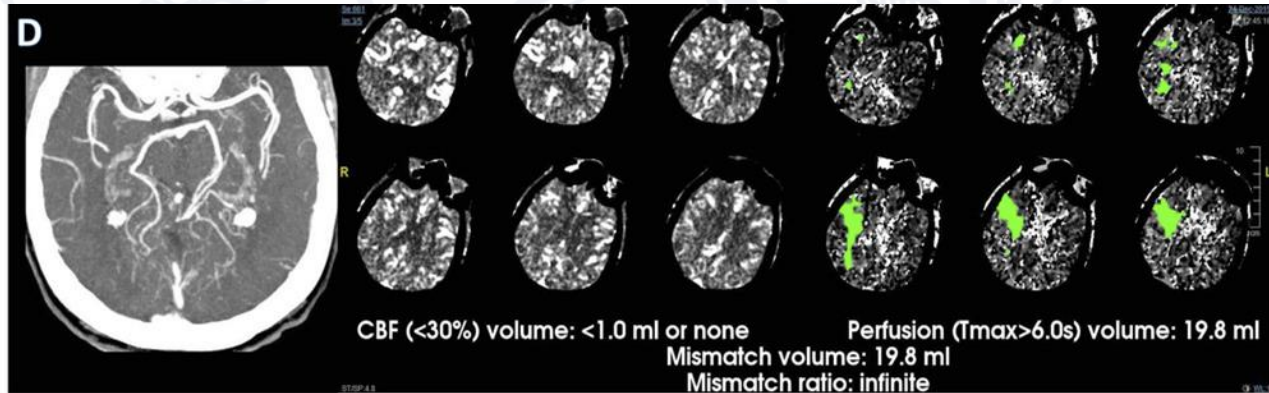
¹Kim, *et al. PLoS One*. 2013;8:e70996

²Nedeltchev, *et al. Stroke*. 2007;38:2531-2535

³Heldner, *et al. J Neurol Neurosurg Psychiatry*. 2015;86:755-760

Predictors of Deterioration

- Large vessel occlusion, proximal > distal
- Collateral quality, cerebral reserve
- Hemodynamic status
- Nature of occlusion? atherosclerotic stenosis vs embolism?



INTRAVENOUS THROMBOLYSIS IN LNS

JAMA | **Original Investigation**

Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits The PRISMS Randomized Clinical Trial

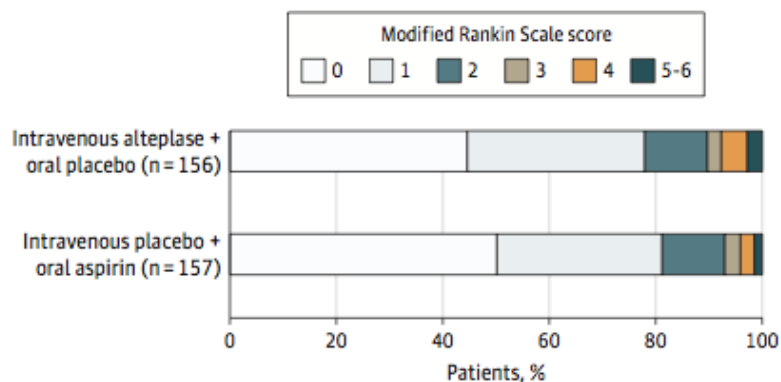
Pooja Khatri, MD, MSc; Dawn O. Kleindorfer, MD; Thomas Devlin, MD; Robert N. Sawyer Jr, MD; Matthew Starr, MD; Jennifer Mejilla, DO; Joseph Broderick, MD; Anjan Chatterjee, MD; Edward C. Jauch, MD, MS; Steven R. Levine, MD; Jose G. Romano, MD; Jeffrey L. Saver, MD; Achala Vagal, MD, MS; Barbara Purdon,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

Khatri, *et al.* JAMA. 2018;320(2):156-166

Table 2. Presenting Event Characteristics

Characteristics	No. (%)	
	Intravenous Alteplase + Oral Placebo (n = 156)	Intravenous Placebo + Oral Aspirin (n = 157)
Rapid improvement of symptoms prior to study treatment administration	8 (5.1)	7 (4.5)
Localization of presenting deficit ^a		
Right hemisphere	75 (48.1)	67 (42.7)
Left hemisphere	59 (37.8)	62 (39.5)
Unknown	19 (12.2)	21 (13.4)
Brainstem/cerebellum	9 (5.8)	18 (11.5)
Final diagnosis		
Acute cerebral ischemia	136 (88.3)	131 (85.6)
Neurovascular mimic ^b	18 (11.7)	22 (14.4)
Ischemic cerebral event etiology ^c	n=138	n=135
Small vessel disease	48 (34.8)	52 (38.5)
Undetermined etiology	40 (29.0)	46 (34.1)
Cardioembolism	20 (14.5)	17 (12.6)
Large artery atherosclerosis	20 (14.5)	10 (7.4)
Other determined etiology ^d	10 (7.2)	10 (7.4)

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



Outcomes	Effect Estimate, Risk Difference or OR (95% CI) ^a
Primary Outcome	
mRS score of 0 or 1, adjusted ^b	-1.1 (-9.4 to 7.3)

Adverse Events	No. (%)	
	Intravenous Alteplase + Oral Placebo (n = 156)	Intravenous Placebo + Oral Aspirin (n = 157)
Primary Adverse Event Assessment		
Symptomatic intracranial hemorrhage within 36 h	5 (3.2)	0

INTRAVENOUS THROMBOLYSIS IN LNS

- Criticisms/limitations
 - Trial terminated early due to slow enrollment by sponsor. Only 313 of the intended 1000 subjects were enrolled
 - Unknown proportion of patients with LVO
 - Important info because IV tPA is not as efficient at recanalizing a LVO, especially the longer the thrombus is (recent *Stroke* study: cutoff 9 mm)
 - Stroke mimics were included
- Conclusion from PRISMS
 - Severe limitations prevent from drawing definitive conclusions
 - **Cannot reliably recommend IV tPA for non-disabling LNS at this point**

BRIDGING THERAPY IN LNS

- Tenecteplase (TNK) gaining momentum as thrombolytic therapy
 - Advantages of TNK: ↑ half-life, ↑ fibrin-specificity and ↑ resistance to PAI than alteplase
 - In EXTEND-IA TNK ¹, TNK achieved higher recanalization at initial angiogram and better functional outcomes at 90 days compared with alteplase
- TNK is being investigated as bridging therapy (thrombolysis followed by thrombectomy) in LNS with LVO in **TEMPO-2**
 - **NIHSS <5 presenting within 12 hours of onset of symptoms with proven occlusion**
 - **TEMPO 1 demonstrated safety and feasibility**

¹ Campbell, et al. *N Engl J Med* 2018; 378:1573-1582

MECHANICAL THROMBECTOMY IN LNS

- No RCT available to guide management
- Only retrospective observational studies and case series with wide variability in methods, inclusion criteria and treatment times
- Many studies have shown benefit or signal towards benefit for MT

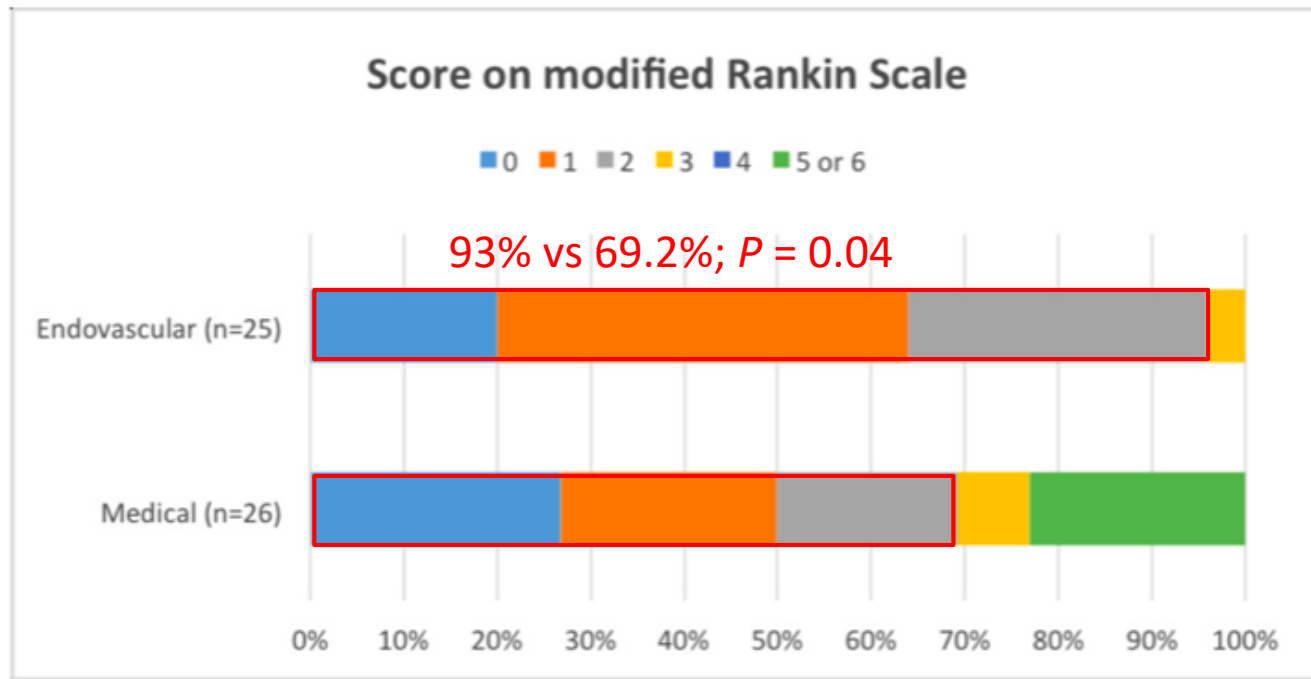


Figure 2 Functional outcome at 90 days according to the score on the modified Rankin Scale (matched populations).

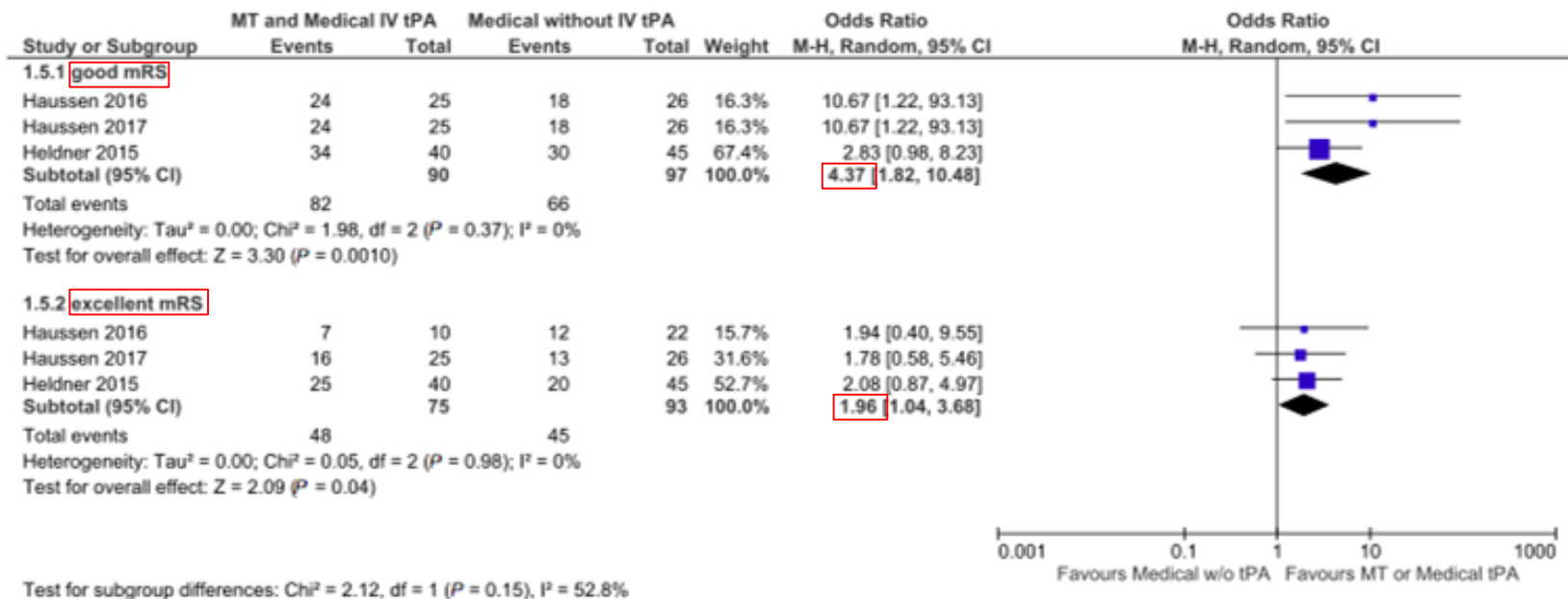
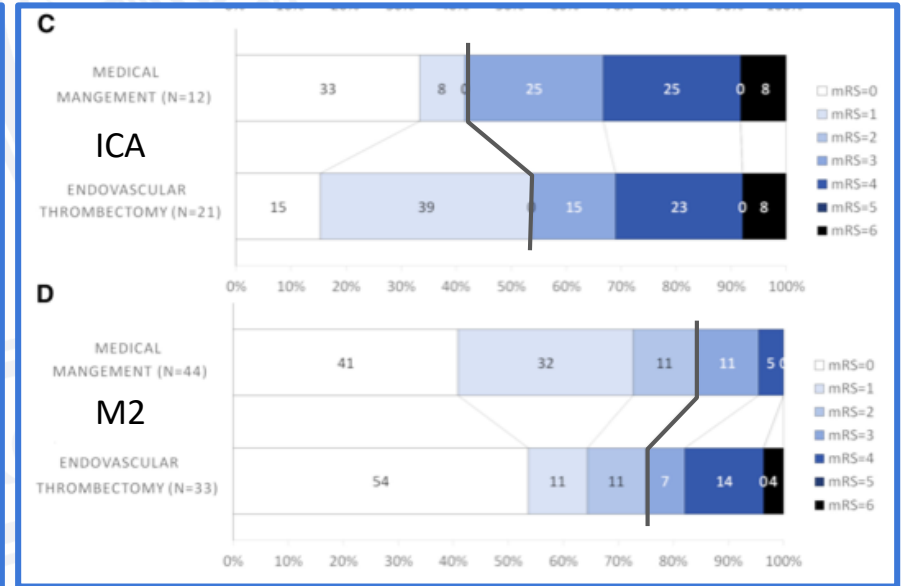
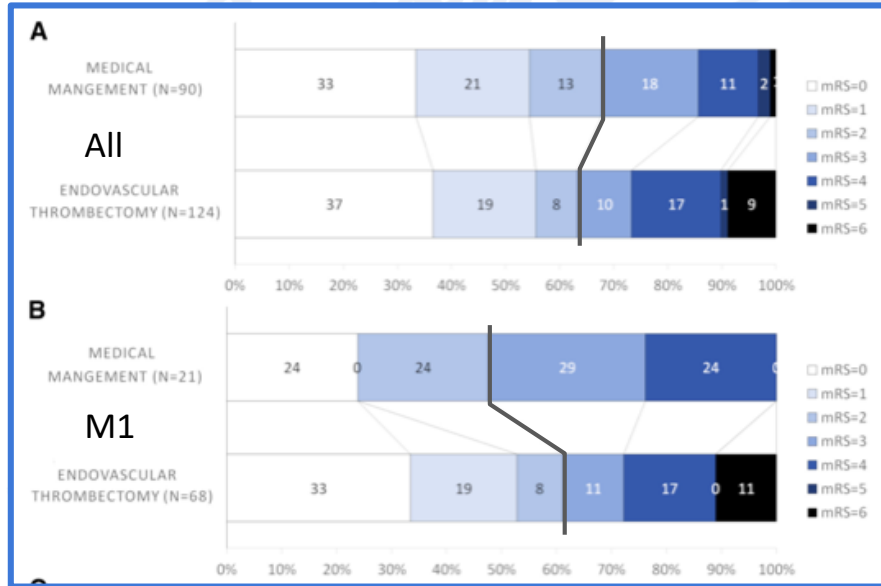


Figure 2. Forest plot of functional outcome at 90 days for mechanical thrombectomy and medical therapy with

intravenous tPA versus medical therapy without intravenous tPA.

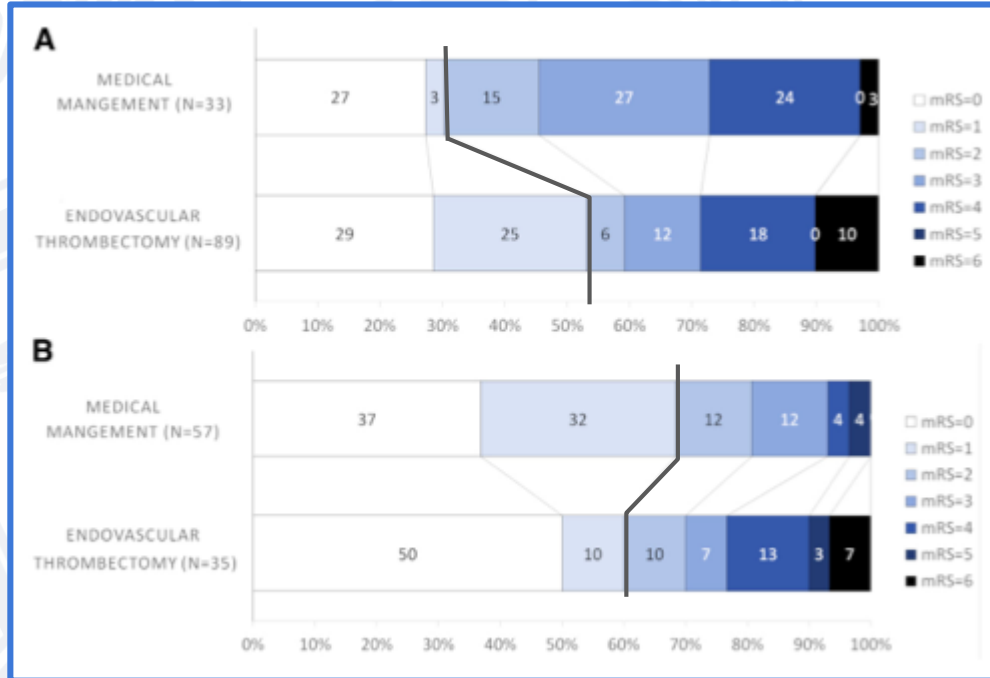
MT in LNS by thrombus location (90d functional outcome)



Sarraj, et al. Stroke. 2018;49:2398-2405

MT in LNS by thrombus location (90d functional outcome)

Proximal
(M1, ICA)



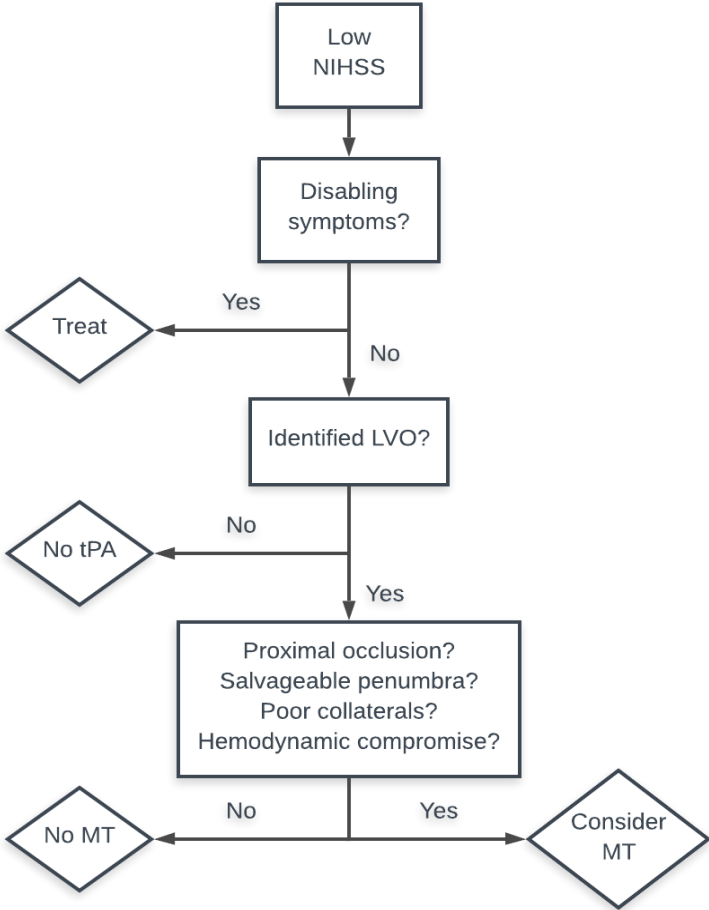
Distal
(M2, M3, M4,
ACA)

MT in LNS by thrombus location (90d functional outcome)

Table 2. Excellent Outcome Rates (mRS, 0–1) and Unadjusted and aORs, Between EVT and Medical Management Only Stratified by Thrombus Location

Thrombus Location	Excellent Outcome (mRS, 0–1), %		Excellent Outcome (mRS, 0–1)			
	EVT	Medical Management	OR (95% CI)	PValue	aOR (95% CI)	PValue
All (n=214)	55.7	54.4	1.05 (0.57–1.93)	0.87	1.30 (0.64–2.64)	0.47
M1 (n=89)	52.8	23.8	3.58 (1.07–11.97)	0.04	3.31 (0.92–11.94)	0.07
ICA (n=33)	53.8	41.7	1.63 (0.33–8.05)	0.54	1.95 (0.35–10.77)	0.44
Proximal* (n=122)	53.1	30.3	2.60 (1.02–6.64)	0.05	2.68 (0.98–7.32)	0.05
M2 (n=77)	64.3	72.7	0.68 (0.24–1.88)	0.45	0.68 (0.23–2.01)	0.48
M3/M4/ACA (n=15)	0	53.8
Distal† (n=92)	60	68.4	0.69 (0.27–1.75)	0.43	0.70 (0.26–1.87)	0.47

PROPOSED ALGORITHM



Take Home messages (1)

- Strokes presenting initially with minor deficits may worsen and lead to long-term disability
- Be aware of factors that can lead to neurological deterioration of a minor stroke, e.g. LVO (proximal), poor collateral circulation
- Heterogeneity/variability in definition of minor strokes and slow enrollment have made it difficult to research this subpopulation
- We are in desperate need of large RCTs to guide adequate treatment in this group

Take Home messages (2)

- IV thrombolysis alone may not be the best therapy for minor stroke
- MT+IV tPA may have a role for minor strokes with LVO
- MT may be beneficial in minor strokes with proximal but not distal LVO
- Use of perfusion imaging and collateral scoring may help select patients who will benefit from acute therapies

Thank you

