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Leaning in to Acute Stroke Care in Resource-Limited Settings

July 22nd, 2022

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Disclaimer

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Disclosures

- I receive grant funding from the Telehealth Network Grant Program through HRSA

Objectives

- Discuss how to remain thorough & efficient with acute code stroke processes in rural settings
- Review tools to support decision-making with regards to stroke diagnosis and reperfusion decisions
- Outline the role of the rural community ED, critical access site and ASRH in the larger stroke system-of-care

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Where I Live & Work…

- **Aging population that values community-based care, yet workforce and geographic challenges the equitable delivery of care**

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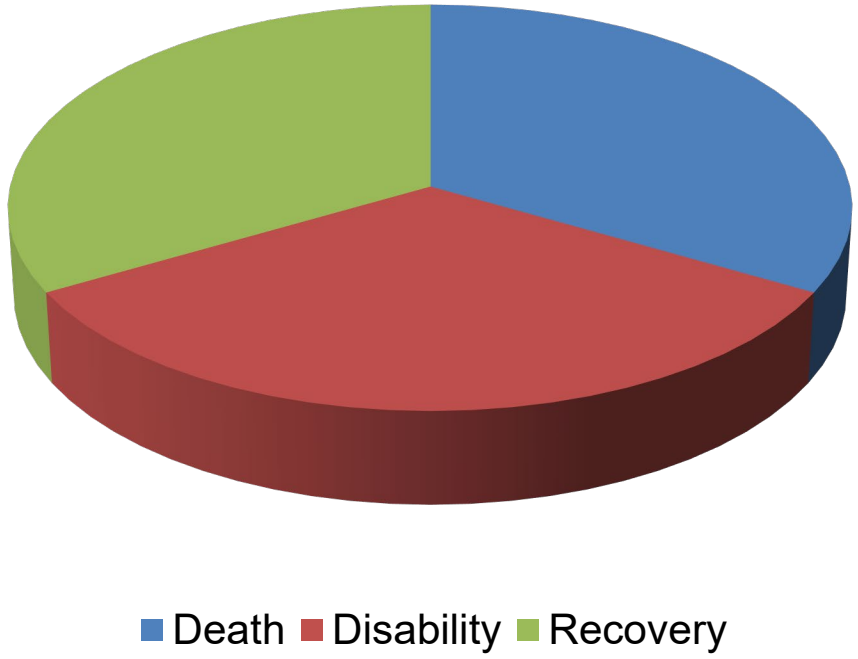
Some Fundamental Truths…

- Time is brain, disability & quality of life
- Designated stroke centers are associated with improved patient outcomes
- Stroke systems-of-care are evolving rapidly and have the potential to markedly reduce the overall burden of disease

Saver JL. Brain 2017
Meretoja A et al. Neurology 2017
Saver JL et al. JAMA 2016
Ganesh A et al. Neurology 2016
Xian Y et al. JAMA 2011
Adeoye O et al. 2019

Justification

- 5th leading cause of death in the US
- Leading cause of disability ($74 billion)
- 17 million strokes per year (85% ischemic)
- Burden of stroke in the US estimated to double by 2050



Towfighi A, Saver JL. Stroke. 2011
Feigin VL, Forouzanfar MH, et al. Lancet 2014
Howard G, Goff DC. Ann NY Acad Sci 2012

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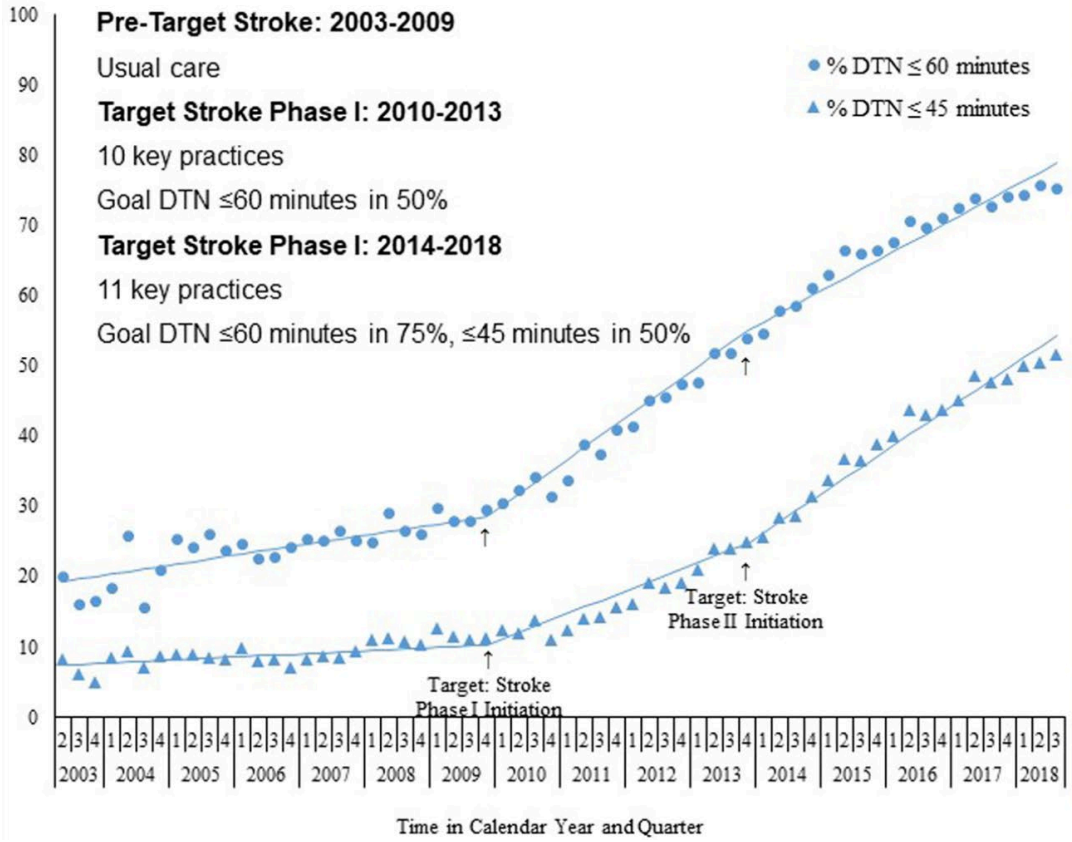
Achieving More Rapid Door-to-Needle Times and Improved Outcomes: Target: Stroke Phase I and Phase II



Measure	Period	Event Rate	Adjusted OR (95% CI)
In-hospital Mortality	Pre-intervention	10.0%	Ref
	Phase I	8.2%	0.84 (0.79-0.89)
	Phase II	6.0%	0.69 (0.64-0.73)
sICH≤36 h	Pre-intervention	5.5%	Ref
	Phase I	4.3%	0.79 (0.73-0.86)
	Phase II	3.4%	0.68 (0.62-0.74)
Discharged to home	Pre-intervention	35.7%	Ref
	Phase I	41.5%	1.21 (1.16-1.26)
	Phase II	49.6%	1.43 (1.38-1.50)
Independent ambulation at discharge	Pre-intervention	41.5%	Ref
	Phase I	44.6%	1.08 (1.02-1.15)
	Phase II	53.3%	1.40 (1.32-1.49)
Disability-free (mRS 0-1) at discharge	Pre-intervention	17.8%	Ref
	Phase I	25.3%	1.11 (0.76-1.61)
	Phase II	31.3%	1.08 (1.01-1.16)

Xian Y et al. Stroke 2021

Almost All Americans Are Now Within 1 Hour of Good Stroke Care

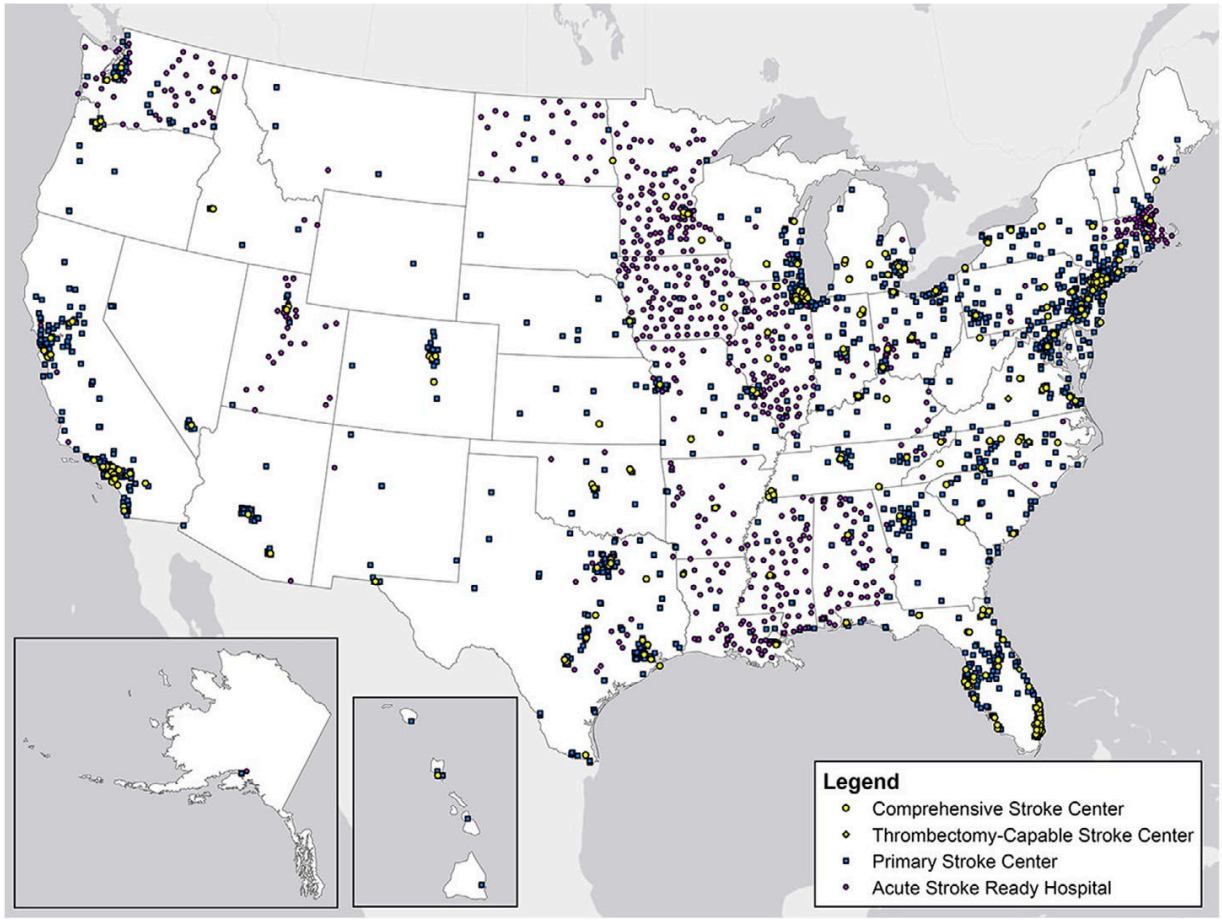
Feb. 3, 2022, at 8:18 a.m.

Save

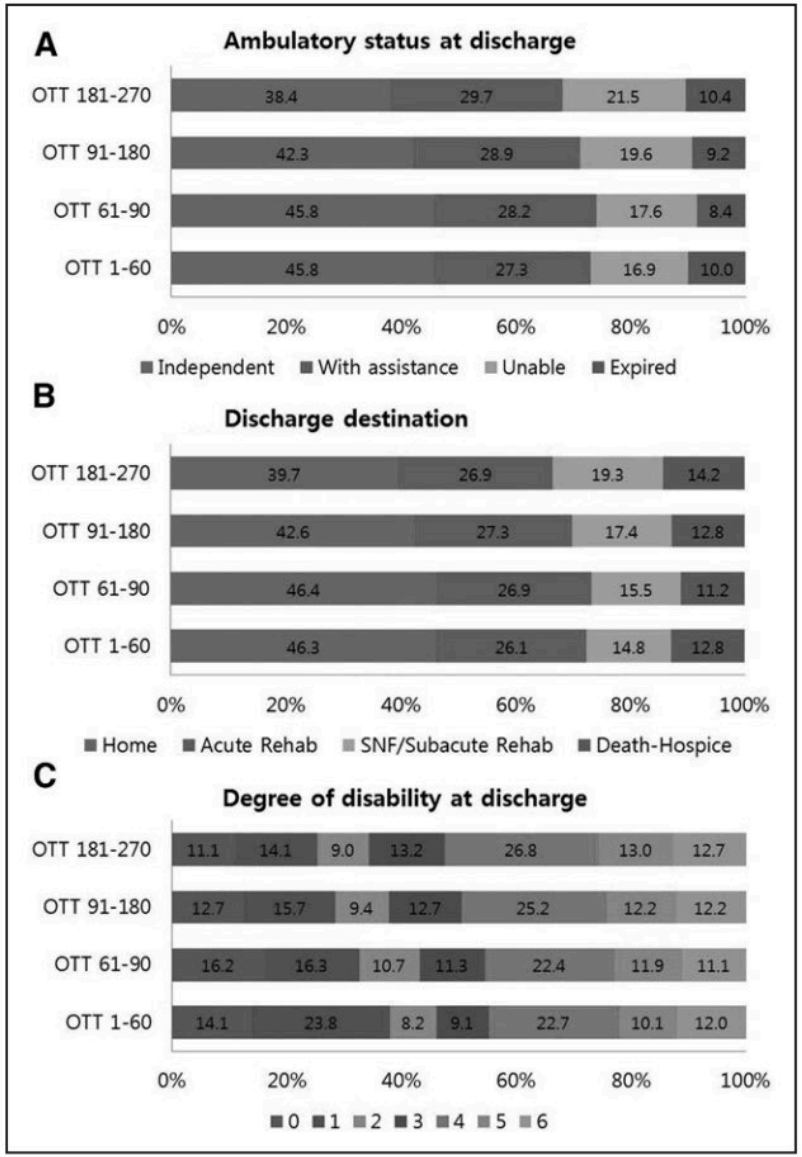
- **91%** within an hour drive time to an ASRH or more
- **96%** within an hour to a telestroke capable facility

2446 (44%) stroke centers

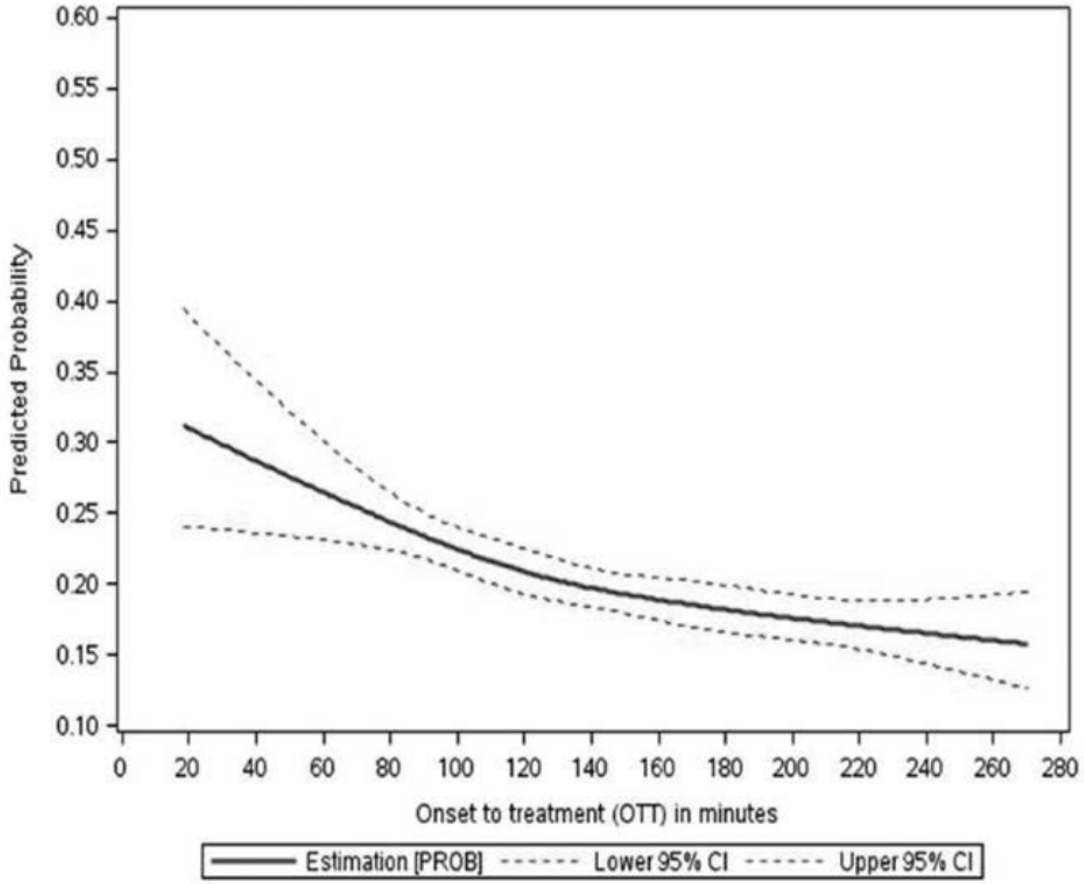
- 297 CSCs
- 14 TCSCs
- 1459 PSCs
- 678 ASRHs



https://www.usnews.com/news/health-news/articles/2022-02-03/almost-all-americans-are-now-within-1-hour-of-good-stroke-care



- **65,384 tPA treated AIS patients**



Kim JT et al. Circulation 2017;135(2):128-39

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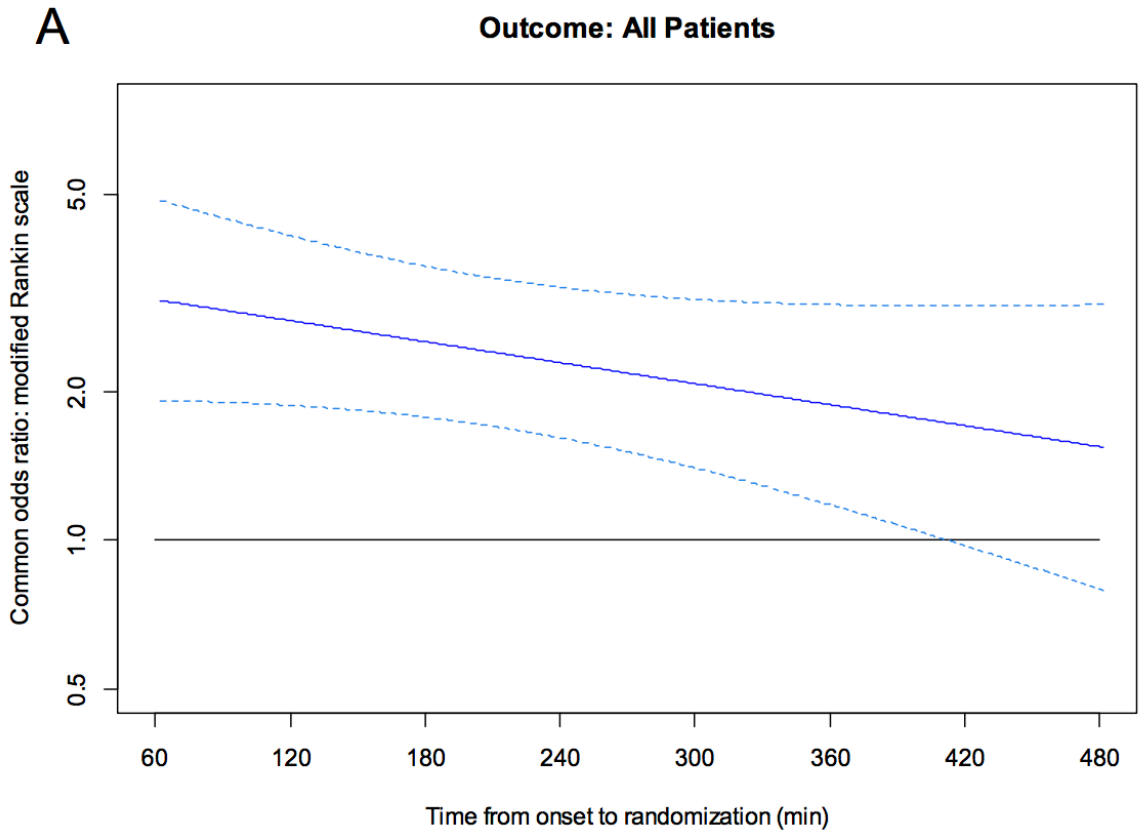
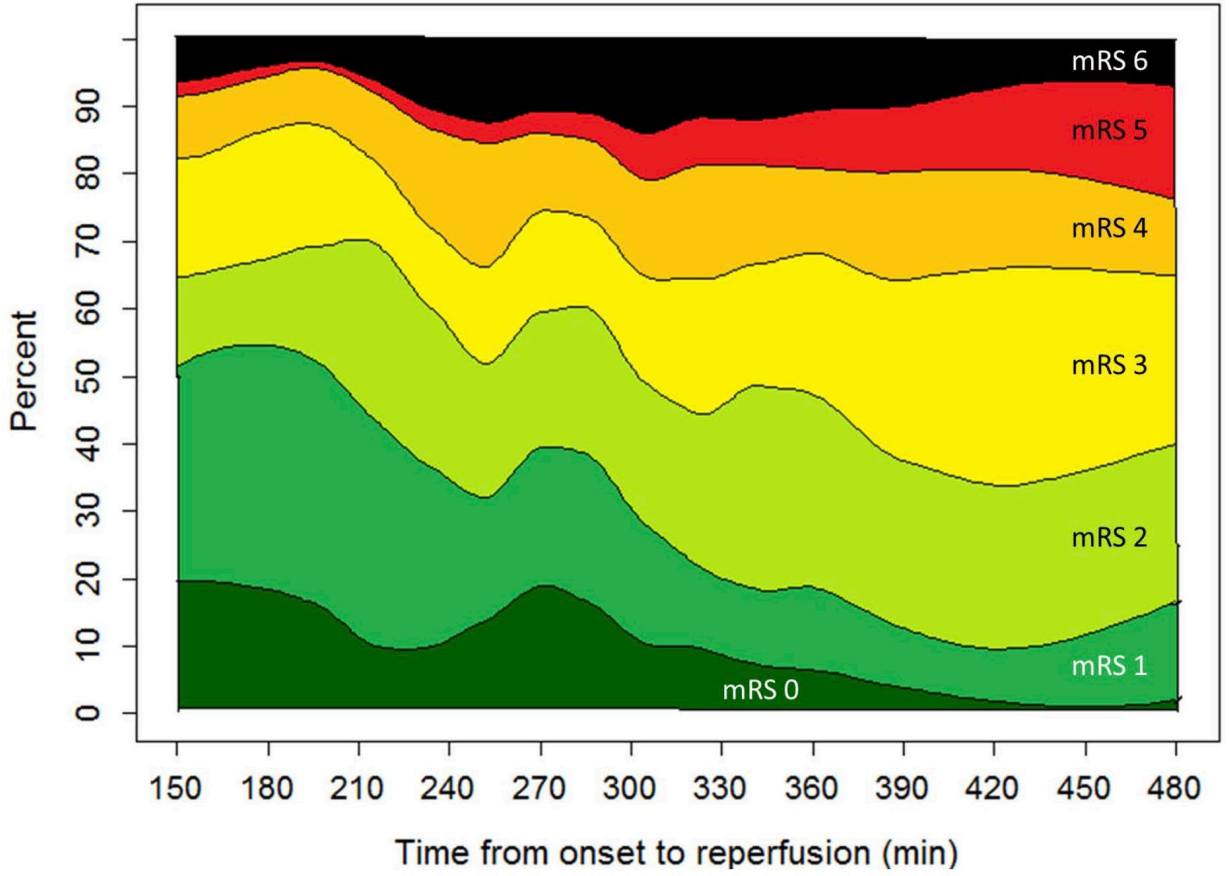
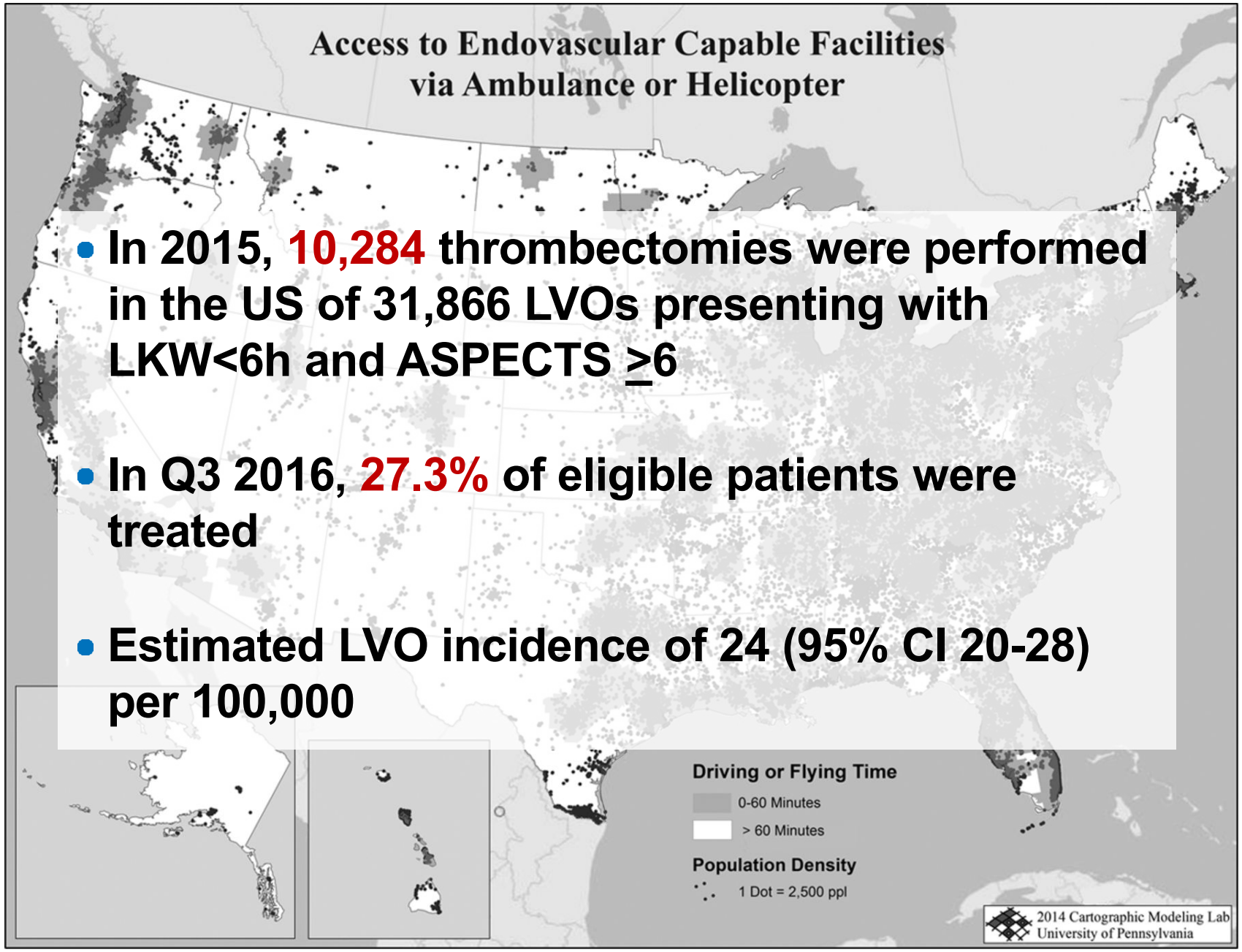
Time Dependent Effect in LVO





Saver JI et al. JAMA 2016



- In 2015, 10,284 thrombectomies were performed in the US of 31,866 LVOs presenting with LKW<6h and ASPECTS ≥6
- In Q3 2016, 27.3% of eligible patients were treated
- Estimated LVO incidence of 24 (95% CI 20-28) per 100,000

Table. Percentage of Americans With 60-Minute Access to r-tPA–Capable Hospitals, Endovascular-Capable Hospitals, and Primary Stroke Centers by Ground and Air Ambulance, Allowing for Crossing State Lines

	60-min Ground Access			60-min Air Access		
	r-tPA Capable, %	Endovascular Capable, %	PSC, %	r-tPA Capable, %	Endovascular Capable, %	PSC, %
Northeast						
New England						
CT	95.6	63.8	89.4	100.0	100.0	100.0
ME	54.5	21.3	31.7	90.0	60.5	88.7
MA	96.3	63.4	9.3	100.0	97.6	96.9
NH	77.1	0.0	0.0	99.6	81.9	74.7
RI	97.5	83.7	96.5	100.0	100.0	100.0
VT	37.1	25.1	25.1	90.7	66.4	66.3
Middle Atlantic						
NJ	98.4	87.0	95.1	100.0	100.0	100.0
NY	91.9	77.4	72.3	99.8	96.0	94.2
PA	85.5	57.8	73.5	100.0	97.5	99.7

Rai AT et al. BMJ 2016
Smith EE et al. Circulation 2017
Adeoye O et al. Stroke 2014
Rai AT et al. SNIS 2017

Reasons for Failure

- Lack of recognition
- Delay to diagnosis
- Inefficient transfer systems-of-care
- ASPECTS decay during inter-facility transfer
  - Occurred in 1/3 of patients (31%) in one study

Mokin M, et al. JNIS 2017

A Difficult Ask in Resource-Limited Settings…

- ✓ **Improve access to care**
- ✓ **Expedite time to diagnosis**
- ✓ **Avoid misdiagnosis**
- ✓ **Consider individual preferences of each patient**
- ✓ **Minimize time to definitive management**

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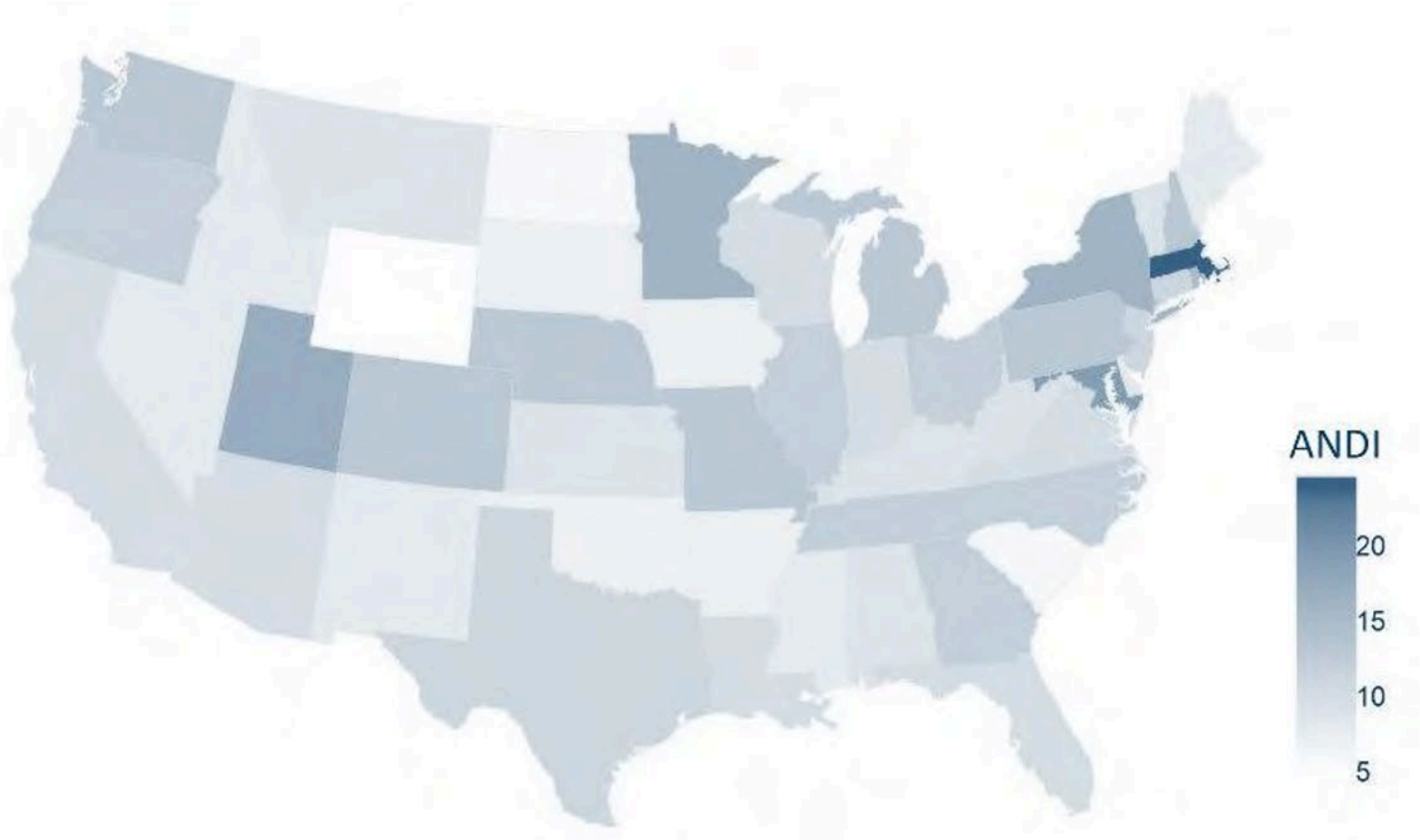
Neurology Deserts Are Common…



Top 20 neurology desert states

Wyoming
North Dakota
South Carolina
South Dakota
Oklahoma
Iowa
Arkansas
Hawaii
New Mexico
Nevada
Mississippi
Maine
Idaho
Delaware
Alabama
Montana
Kansas
Vermont
West Virginia
Kentucky

Roa A, Eaton F. Dementia Neurology Deserts and Long-Term Care Insurance Claims Experience in the United States. Society of Actuaries May 2021. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.neurocern.com/wp-content/uploads/2021/05/2021-dementia-neurology-deserts-1.pdf

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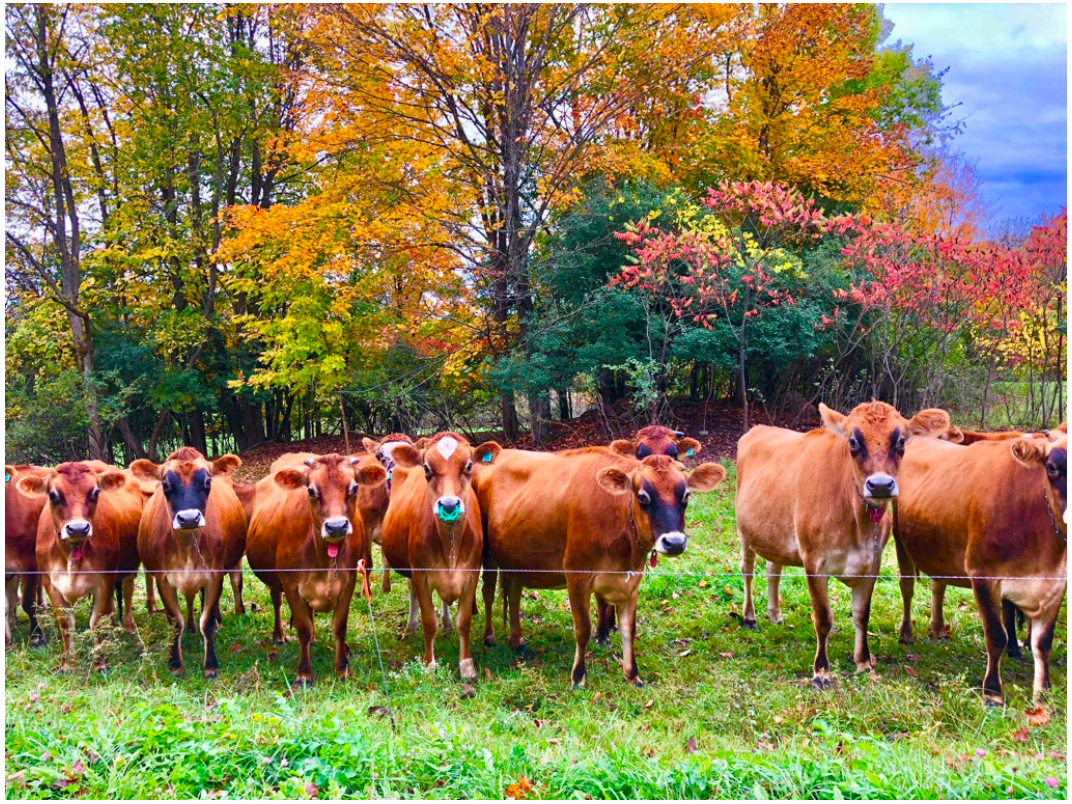
How EM & EMS Can Safely & Effectively Lead a Code Stroke Response:



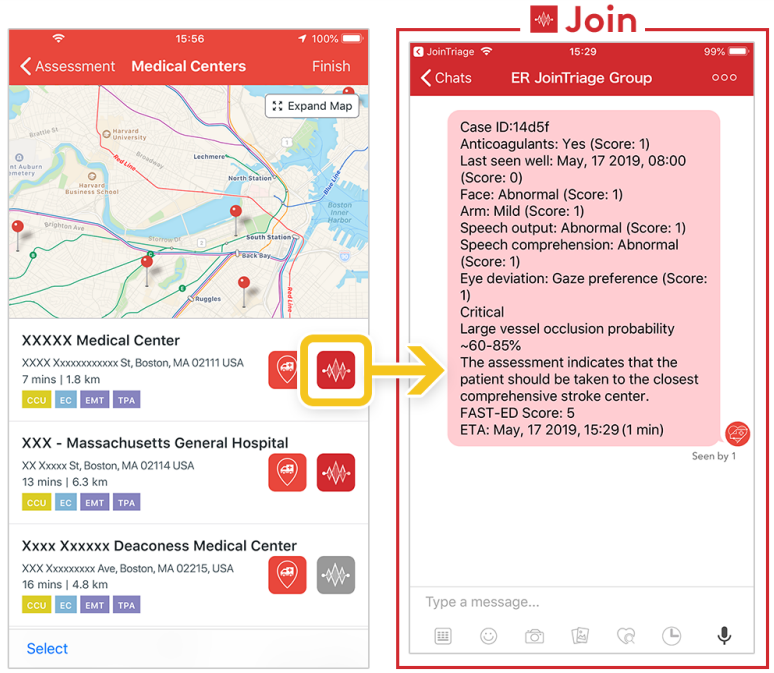
- ✓ **Stroke screening & severity grading in the field**
- ✓ **Regional destination protocols**
- ✓ **Drip and ship or Mothership?**
- ✓ **Grease the wheels to reduce the friction**
- ✓ **Advanced imaging capabilities?**

Field Triage

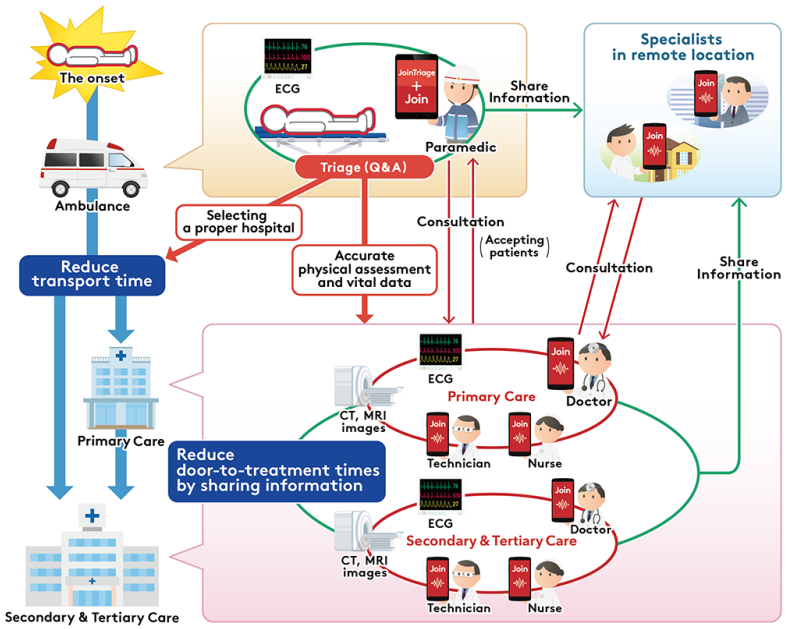
- AHA Mission: Lifeline severity-based stroke triage for EMS
- Centralized & Coordinated Dispatch
- Mobile Endovascular Teams
- Automated decision support for destination determination

	3ISS	LAMS	CPSSS	VAN	PASS	FAST-ED	RACE
LOC	*		*		*		
Gaze	*		*	*	*	*	*
Face		*				*	*
Arm	*	*	*	*	*	*	*
Grip		*					
Leg							*
Aphasia				*		*	*
Neglect				*		*	*

Perez de la Ossa N et al. Stroke 2016



Emergency Medical Information Sharing Image



Large Vessel Occlusion Scales Increase Delivery to Endovascular Centers Without Excessive Harm From Misclassifications

Table 1. Overall Agreement of LVO Scales With CT Imaging

Scale	Accuracy	Kappa (95% CI)	Sens	Spec	PPV	NPV	AUC	DOR
RACE ≥5	0.86	0.51 (0.41–0.60)	0.66	0.90	0.48	0.93	0.78	17.50
LAMS ≥4	0.83	0.43 (0.34–0.52)	0.66	0.86	0.48	0.93	0.76	11.80
FAST-ED ≥4	0.85	0.49 (0.40–0.58)	0.70	0.88	0.48	0.92	0.79	16.40
PASS ≥2	0.81	0.43 (0.34–0.52)	0.71	0.84	0.45	0.93	0.77	12.40
CPSSS ≥2	0.81	0.35 (0.26–0.45)	0.56	0.86	0.42	0.91	0.71	7.54

Prevalence =14.5%. AUC indicates area under receiver-operator curve value; CI, confidence interval; CPSSS, Cincinnati Prehospital Stroke Severity Scale; CT, computed tomography; DOR, diagnostic odds ratio; FAST-ED, Field Assessment Stroke Triage for Emergency Destination; LAMS, Los Angeles Motor Scale; LVO, large vessel occlusion; NPV, negative predictive value; PASS, Prehospital Acute Stroke Severity scale; PPV, positive predictive value; RACE, Rapid Arterial Occlusion Evaluation; Sens, sensitivity; and Spec, specificity.

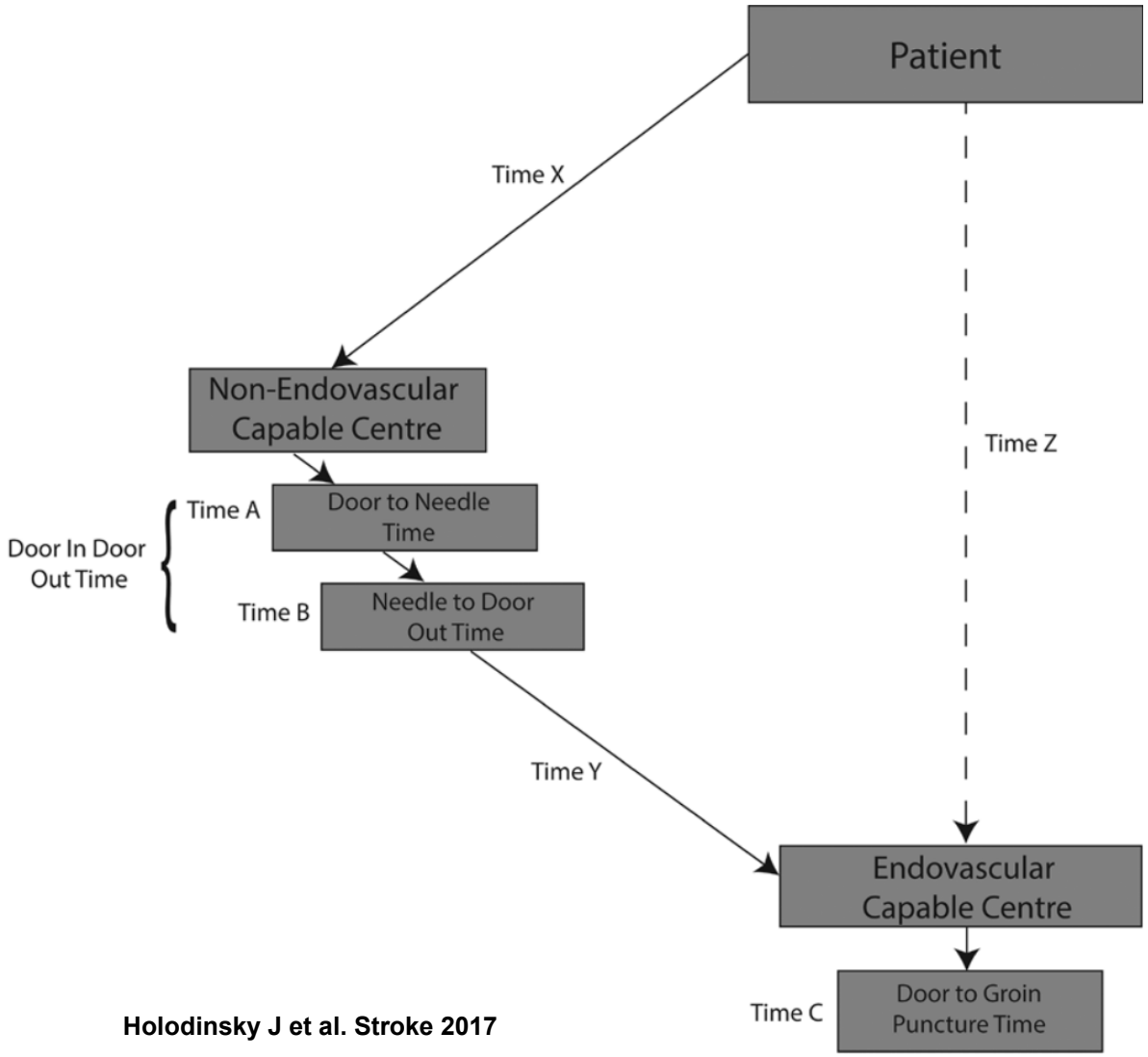
Zhao H et al. Stroke 2017

Cortical Symptoms are the Most Predictive

Group A (n=543)	LVO (n=181)	No LVO (n=362)	SEN	SPE	PPV	NPV	ACC
Hemipareis	153	170	0.85 (0.78–0.89)	0.53 (0.48–0.58)	0.47 (0.42–0.53)	0.87 (0.82–0.91)	0.64
Any cortical symptom	165	108	0.91 (0.86–0.95)	0.70 (0.65–0.75)	0.60 (0.54–0.66)	0.94 (0.90–0.97)	0.77
Aphasia	85	65	0.47 (0.40–0.55)	0.82 (0.78–0.86)	0.57 (0.48–0.65)	0.76 (0.71–0.80)	0.70
Neglect/ gaze deviation	137	65	0.76 (0.69–0.82)	0.82 (0.78–0.86)	0.68 (0.61–0.74)	0.87 (0.83–0.90)	0.80
Cortical symptom AND hemiparesis	142	67	0.79 (0.72–0.84)	0.82 (0.77–0.85)	0.68 (0.61–0.74)	0.88 (0.84–0.92)	0.80
Cortical symptom OR hemiparesis	176	212	0.97 (0.93–0.99)	0.41 (0.36–0.47)	0.45 (0.40–0.51)	0.97 (0.92–0.99)	0.60
	MT (n=109)	No MT (n=434)	SEN	SPE	PPV	NPV	ACC
Hemiparesis	95	228	0.87 (0.79–0.93)	0.48 (0.43–0.52)	0.29 (0.25–0.35)	0.94 (0.89–0.96)	0.55
Any cortical symptom	98	175	0.90 (0.82–0.95)	0.60 (0.55–0.64)	0.36 (0.30–0.42)	0.96 (0.93–0.98)	0.66
Aphasia	44	106	0.40 (0.31–0.50)	0.76 (0.71–0.80)	0.29 (0.22–0.37)	0.84 (0.79–0.87)	0.69
Neglect/gaze deviation	87	115	0.80 (0.71–0.87)	0.74 (0.69–0.78)	0.43 (0.36–0.50)	0.94 (0.90–0.96)	0.75
Cortical symptom AND hemiparesis	89	120	0.82 (0.73–0.88)	0.72 (0.68–0.77)	0.43 (0.36–0.50)	0.94 (0.91–0.96)	0.74
Cortical symptom OR hemiparesis	104	284	0.95 (0.90–0.98)	0.35 (0.30–0.39)	0.27 (0.23–0.32)	0.97 (0.92–0.99)	0.47

Lena-Alexandra B et al. Stroke 2018

Drip n’ Ship or Mothership?



Holodinsky J et al. Stroke 2017

- **<u>Modelling dependent on:</u>**
  - D2N and DIDO times at PSC/ASRH
  - D2N and D2G times at TSC/CSC
  - Reperfusion rates at TSC/CSC

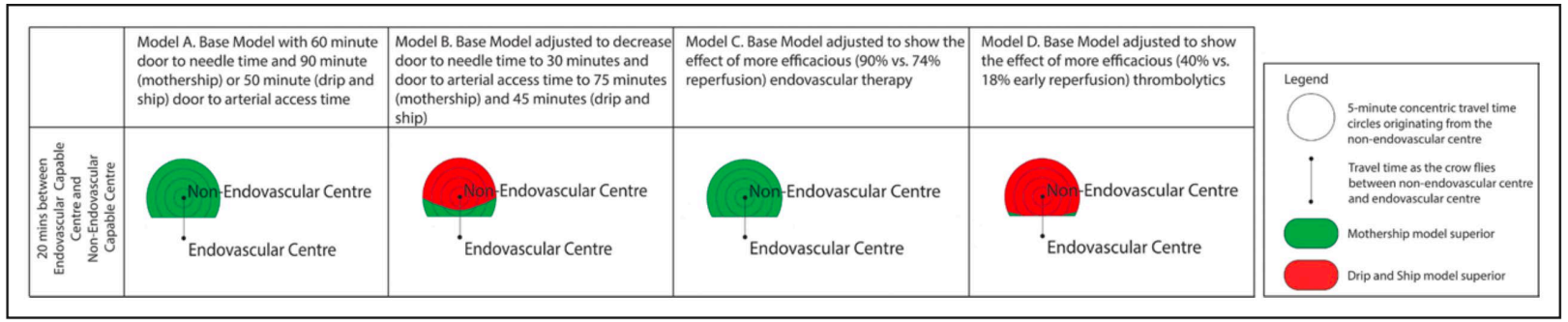
Model Favors Mothership when recanalization rates ~90%

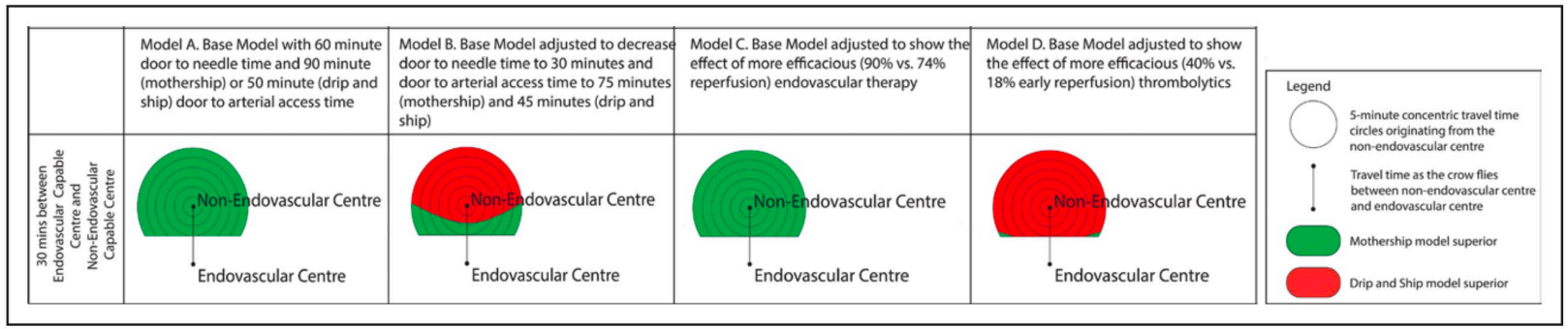
20min

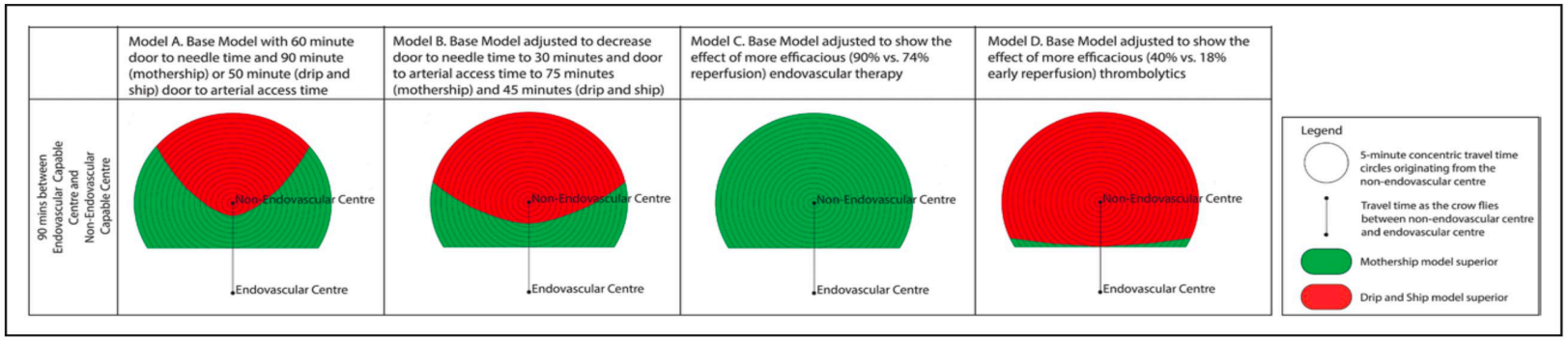
30min

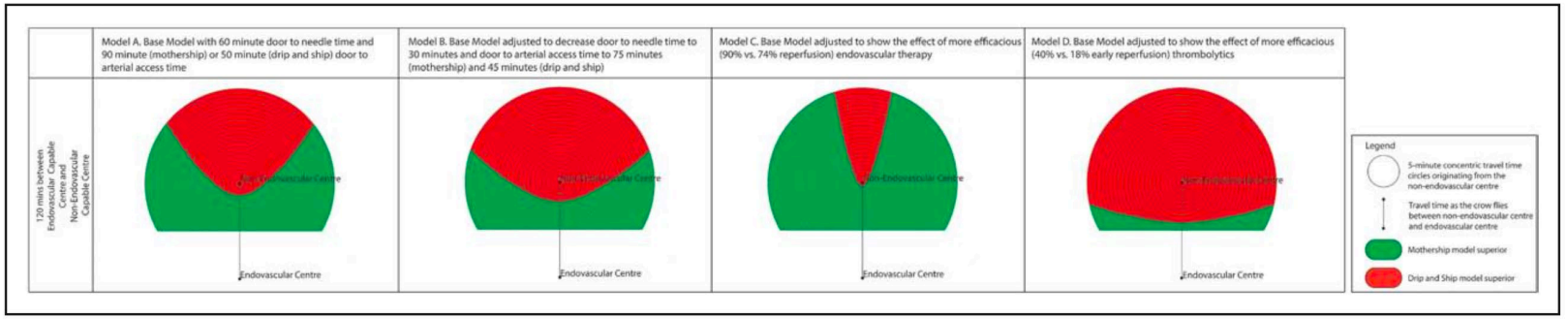
90min

120min









Holodinsky J et al. Stroke 2017

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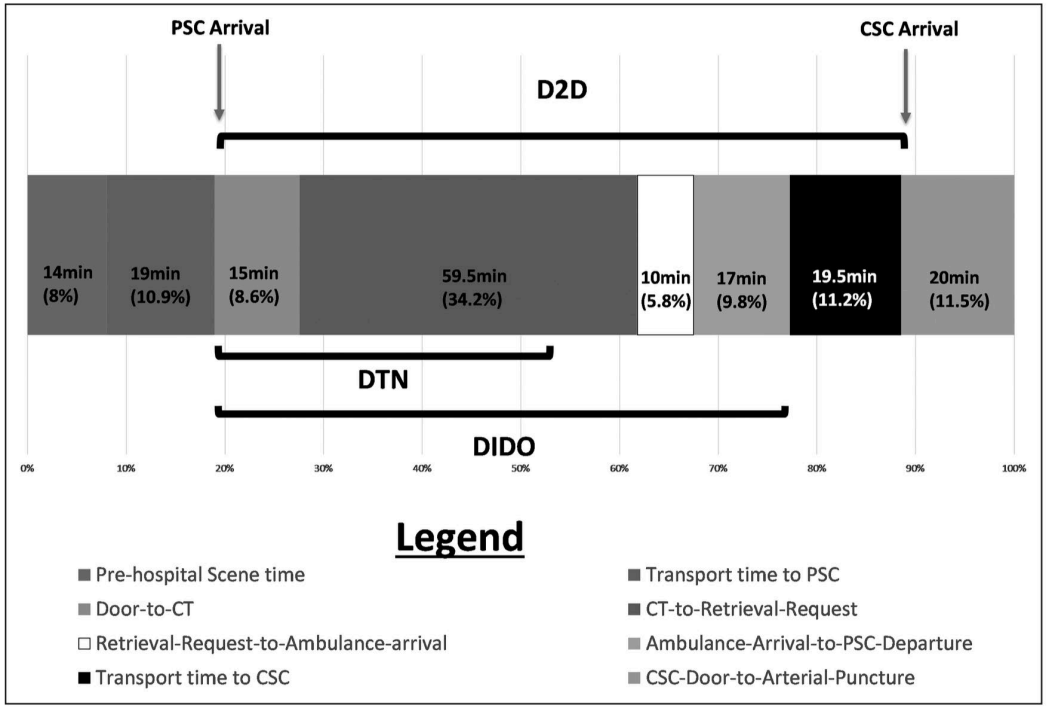
"No Brainer"

- **Conditions required for drip n' ship to be preferred:**
  - ✓ **Longer onset-to-first medical response**
  - ✓ **PSC D2N times < 30 min**
  - ✓ **PSC DIDO times < 50 min**
  - ✓ **CSC D2N times >60 min**
  - ✓ **CSC Door-to-reperfusion time >200 min**
  - ✓ **Transport time > 45 min**



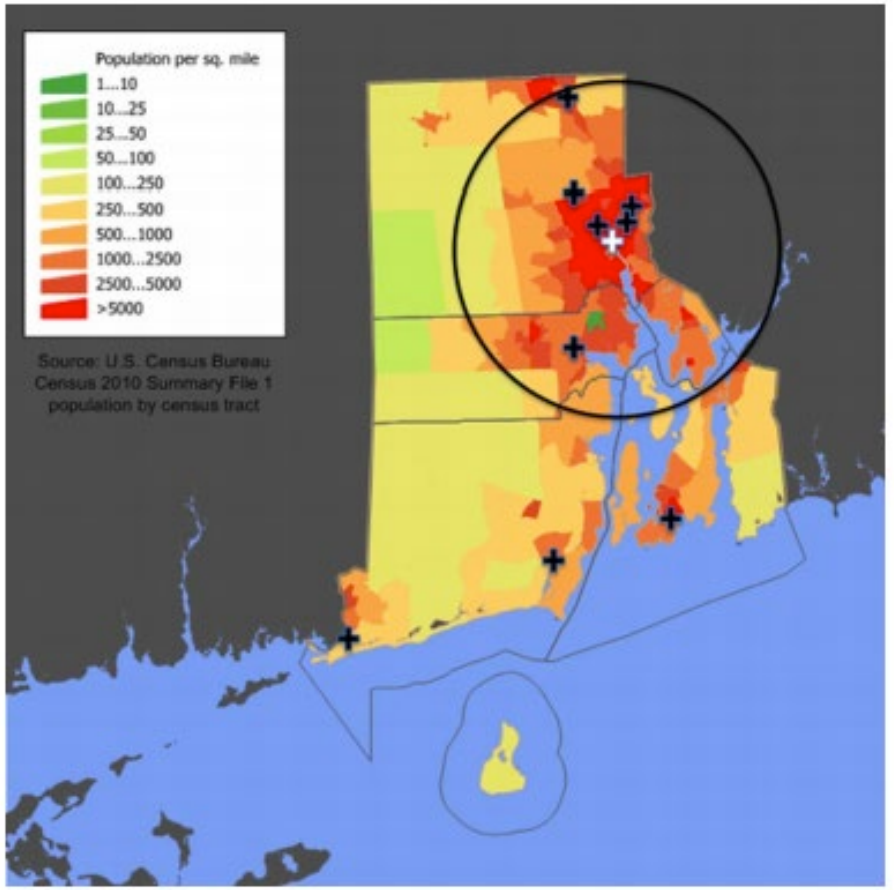
Milne SW et al. Stroke 2017

Ng FC et al. Stroke 2017

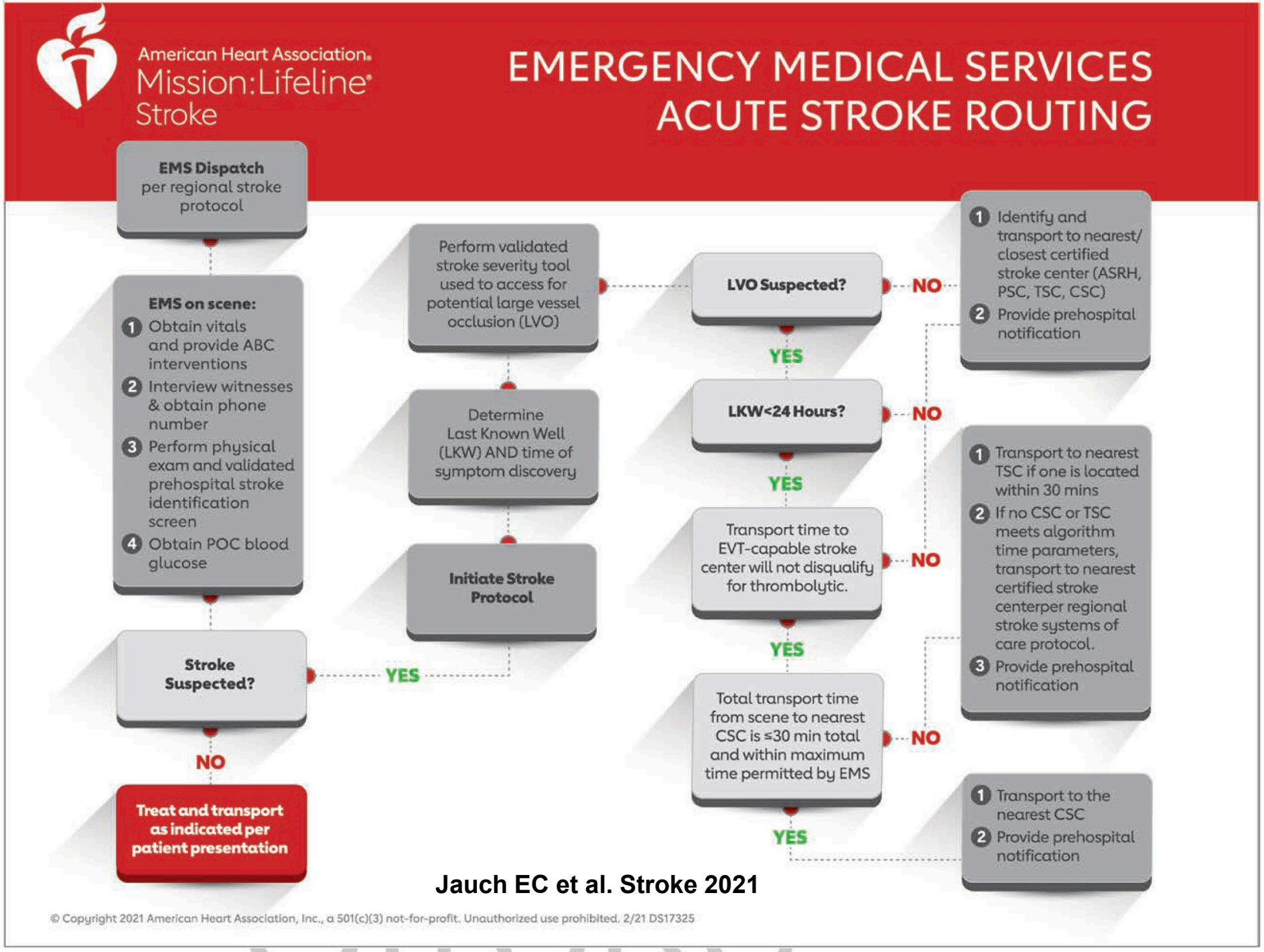
Developing a statewide protocol to ensure patients with suspected emergent large vessel occlusion are directly triaged in the field to a comprehensive stroke center: how we did it

Mahesh V Jayaraman,[1,2,3] Arshad Iqbal,[4] Brian Silver,[2] Matthew S Siket,[5] Caryn Amedee,[2] Ryan A McTaggart,[1] Gino Paolucci,[5] Jason Rhodes,[6] John Potvin,[7] Megan Tucker,[8] Nicole Alexander-Scott[6]

- **State Stroke Task Force Initiative**
- **Implementation of EMS LAMS**
- **Destination protocols**
- **Streamlined inter-facility transfer process**



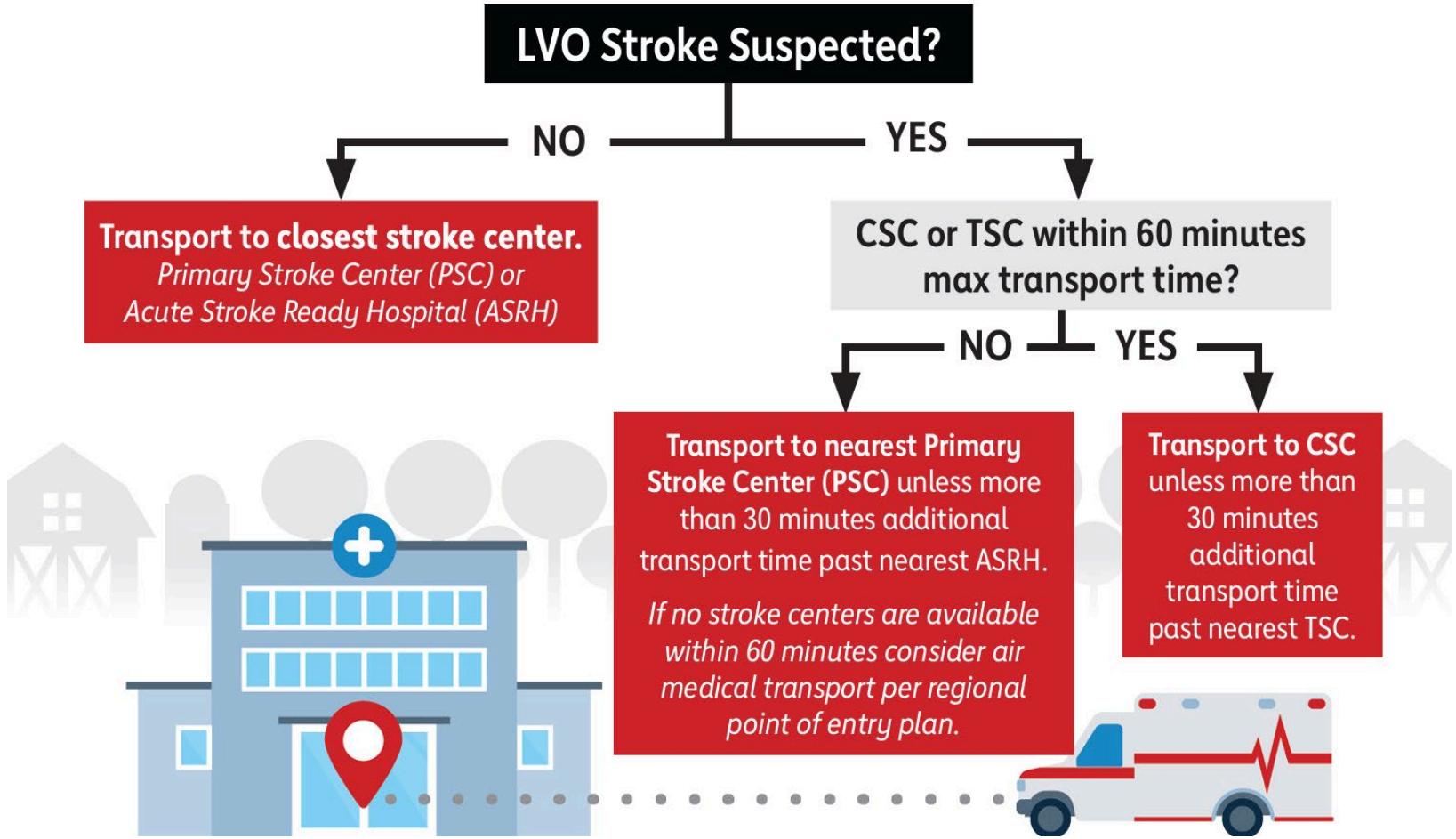
Jayaraman et al JNIS 2016



Jauch EC et al. Stroke 2021

American Stroke Association.
A division of the American Heart Association.
Together to End Stroke®

Stroke Rural Transport Recommendations



chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.stroke.org/-/media/Stroke-Files/EMS-Resources/Stroke-Destination-Change-032021/DS17297_ASA-Stroke-Transport-Graphics_Rural-Final.pdf

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Balance SNS & SPC…Think of Distributive Justice

EMPOWER & SUPPORT THE TEAM:

- Potential reperfusion decision?
- Deficits ongoing, focal & disabling?
- Evidence of a clear mimic?
- Are symptoms positive or negative?

UVMHN STROKE ALERT ACTIVATION CRITERIA

Activate STROKE ALERT if

Obtain LKW

All Stroke Alerts must have a confirmed time LKW < 24 hours ago

1. Any new, ongoing focal neurologic deficit of <4.5 hours duration & potential tPA candidate

or

2. Any new, ongoing significant neurologic deficit <24 hours duration, such as:
   - ☐ **NIHSS>4** or
   - ☐ **Prehospital FAST-ED scale 4-5**
   - ☐ **Unilateral weakness** (face, arm, or leg) or
   - ☐ **Visual field cut** or
   - ☐ **Aphasia** or **Dysarthria**
   - ☐ **Neglect**

☐ **ED PHYSICIAN:** Briefly assess ABCs to ensure airway & hemodynamic stability and confirm the presence of ongoing focal stroke symptoms, then enter orders using the 'ED STROKE ORDERSET' including appropriate imaging

☐ **NEUROLOGY TEAM:** Perform brief assessment of ongoing focal neurologic deficits (NIHSS) and determine whether perfusion imaging is indicated. Confirm LKW and any tPA contraindications

☐ **ED NURSING:** Obtain POCT glucose. Ensure working peripheral IV appropriate for CTA and obtain patient weight prior to CT

☐ **REGISTRATION:** Quickly register the patient

Spend a Moment Considering Atypical & Subtle Presentations

Acute Dizziness Triage Algorithm

1. Does the patient have acute and sustained dizziness of <24 hours duration?

- As opposed to episodic or triggered episodes that completely resolve between events. **Only abrupt onset and sustained dizziness that has not resolved should be considered as a possible acute stroke**

Yes

2. Is there any additional neurologic deficit (except horizontal nystagmus)?

- Deficits may be subtle. Examples include: double vision or vision loss, slurred speech, inability to sit or stand independently, ataxia, vertical or direction-changing nystagmus, dysmetria (on finger-to-nose or heel-to-shin test), loss of coordination, unilateral weakness or sensory loss, decreased level of consciousness or inattention/neglect

Yes

CODE STROKE

No

3. Are signs of a non-stroke diagnosis present?

- Examples include, but are not limited to: cardiac arrhythmia, hypotension, intoxication

Yes

Not likely an acute stroke - triage appropriately

No

4. Are signs of peripheral vertigo present?

- Including horizontal, unidirectional nystagmus, which should always be present in patients with acute and ongoing vertigo from a peripheral cause. Tinnitus and unilateral ear fullness are also suggestive. The ED provider should consider performing the full HINTS exam to differentiate central from peripheral causes.
- **HINTS** stands for **H**ead **I**mpulse test, **N**ystagmus, and **T**est of **S**kew. The presence of horizontal, unidirectional nystagmus AND a positive head impulse test AND the absence of vertical skew deviation confirms a peripheral cause (such as vestibular neuronitis)

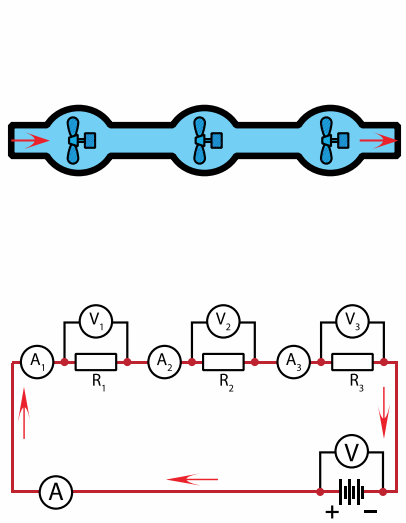
Yes

CODE STROKE

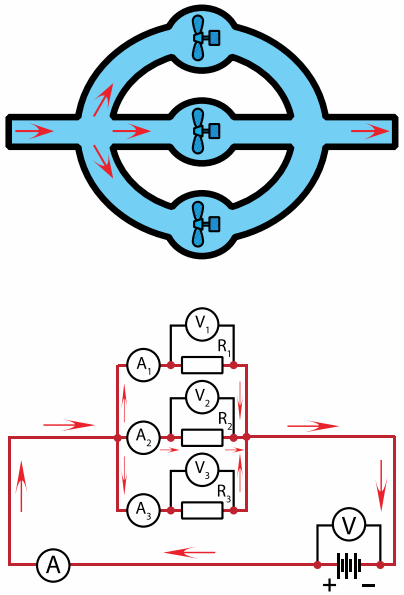
No

Last updated 7/31/18

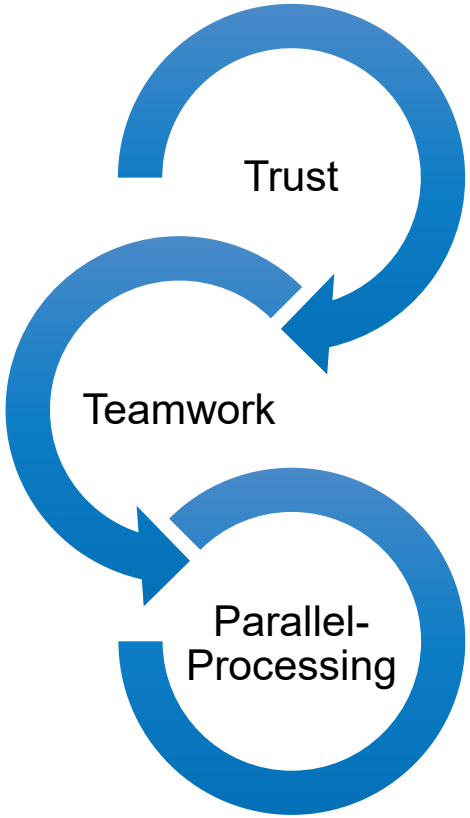
Work in Parallel – Singularly Activate



$$R = R_1 + R_2 + R_3;$$
$$U = U_1 + U_2 + U_3;$$
$$I = I_1 = I_2 = I_3.$$



$$\frac{1}{R} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3};$$
$$I = I_1 + I_2 + I_3;$$
$$U = U_1 = U_2 = U_3.$$



Goyal M et al. Stroke 2014

- EMS
- ED Provider
- ED Nurse
- Registration
- Radiology
- Lab
- Tele-Neurology?
- Pharmacy?
- ED Tech?

Minimize steps & handoffs

WHAT MAKES SENSE FOR YOU?

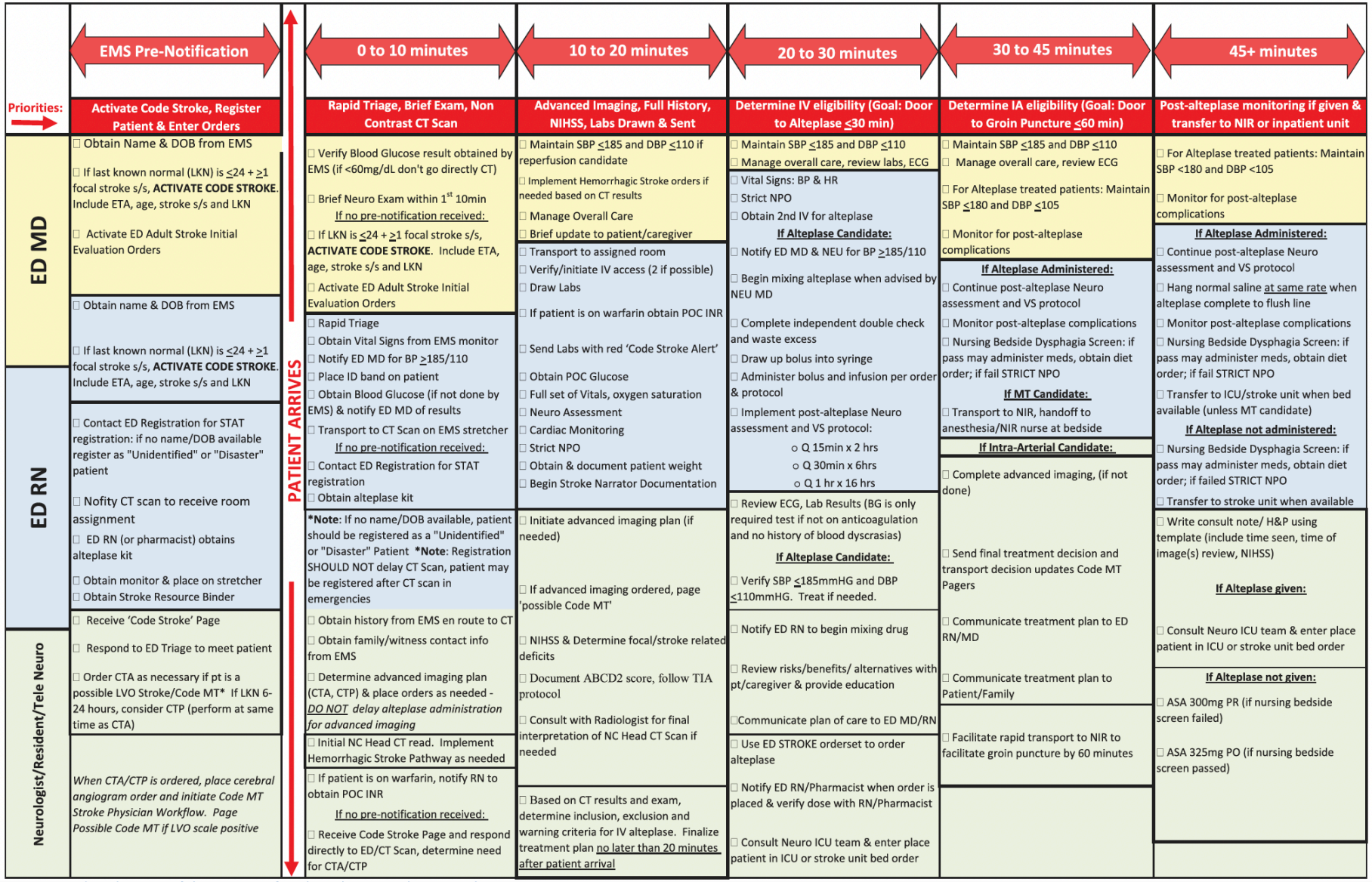
- Can you collect data prior to arrival?
- Designated stroke pitstop?
- ED Resource nurse?
- Stretcher scale outside of CT?
- One-stop for all imaging
- tPA mixing at the bedside or in pharmacy?
- Eliminate excessive checkbacks?
- Hold EMS for possible re-routing?
- Early / one call activation of NIR team?

Cut the fat!

FOCUS ON WHAT MATTERS MOST!

- Old habits die hard..

Design a Process, Test & Refine



Adapted courtesy of The University of North Carolina Comprehensive Stroke Center

Ashcraft S et al. Stroke 2021

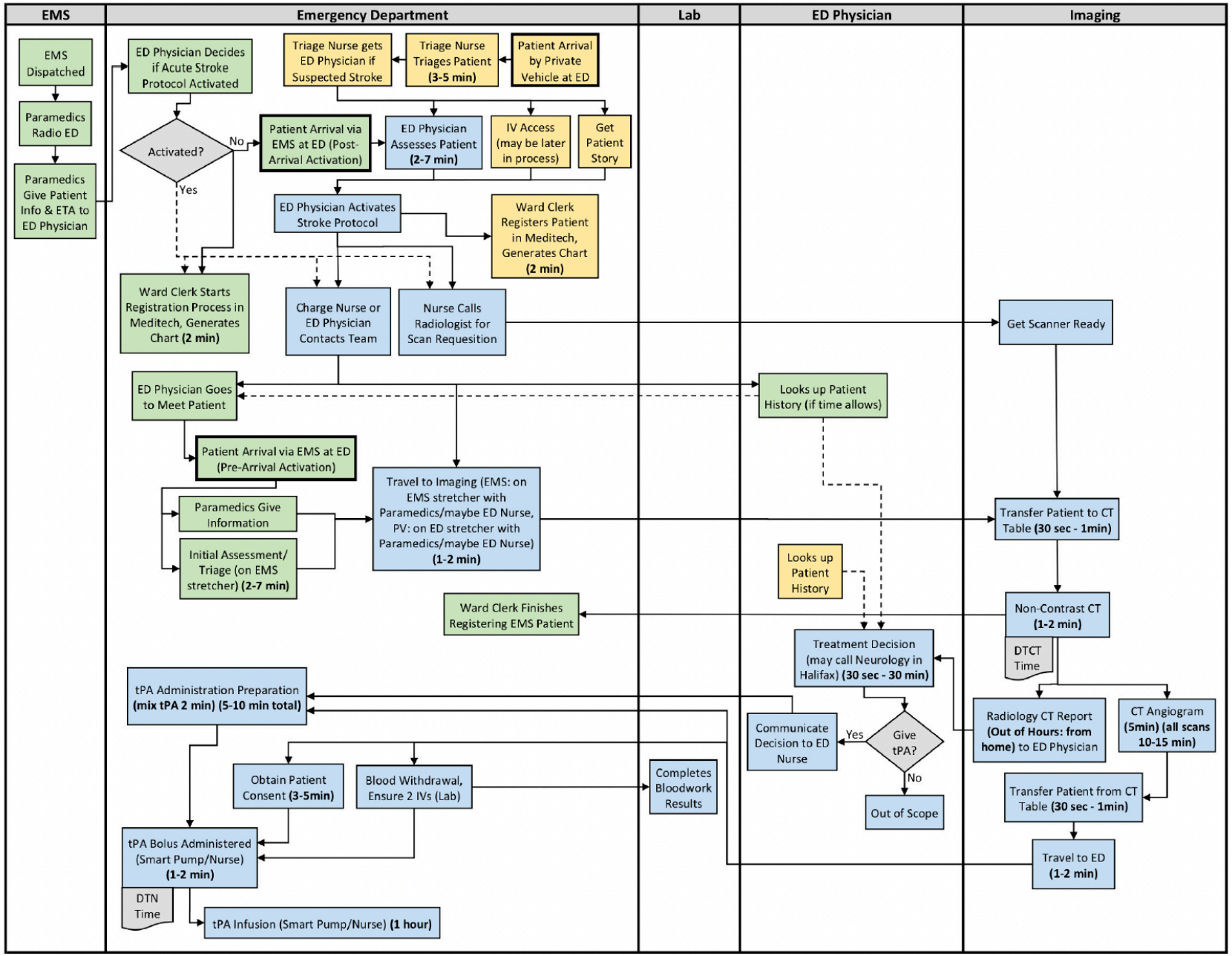
Analysis of Thrombolysis Process for Acute Ischemic Stroke in Urban and Rural Hospitals in Nova Scotia Canada

	Suggested Improvements
	Pre-hospital
Site 1 (Urban)	• More direct information from paramedics (patient identity, clarity of problem, when possible more lead-time) • Modern secure telecom/video streaming systems for transmission of information of paramedic's assessment • EMS to put in two IVs before arriving to ED
Site 2 (Rural)	• EMS to automatically communicate patient identifiers • EMS getting patient's next of kin information and instructing them to go directly to hospital (or being easily accessible via their phone)
Site 3 (Rural)	• EMS triage • EMS availability
	Hospital-based

Site 1 (Urban)	• Stroke nurse available at all times (tPA administered in CT department)
	  ○ Alternatively, have an ED nurse travel with patient to imaging (tPA administered in CT department)
	  ■ tPA stored within CT department in locked drug cupboard
	• Use INR point-of-care machine prior to imaging
	• Wait to collect blood sample until after imaging

Site 2 (Rural)	• Obtain INR point-of-care machine • Have patient's medication list automatically printed out (currently done by ED physician) • Bloodwork collected and 2nd IV put in on EMS stretcher before imaging • Obtain 2nd CT scanner • Improve communication among healthcare professionals • Increase emphasis on continuing education
Site 3 (Rural)	• Mix tPA and have treatment discussion while patient in scanner • Remove NG tube and Foley catheter requirement before tPA administration • Registration clerk and CT technologist in-hospital at all times • Clarification on which patients require CTA scan • Increase education piece to improve ED physician comfort with giving tPA

Bulmer T et al. Front Neurol 2021



Bulmer T et al. Front Neurol 2021

Shifting Bottlenecks

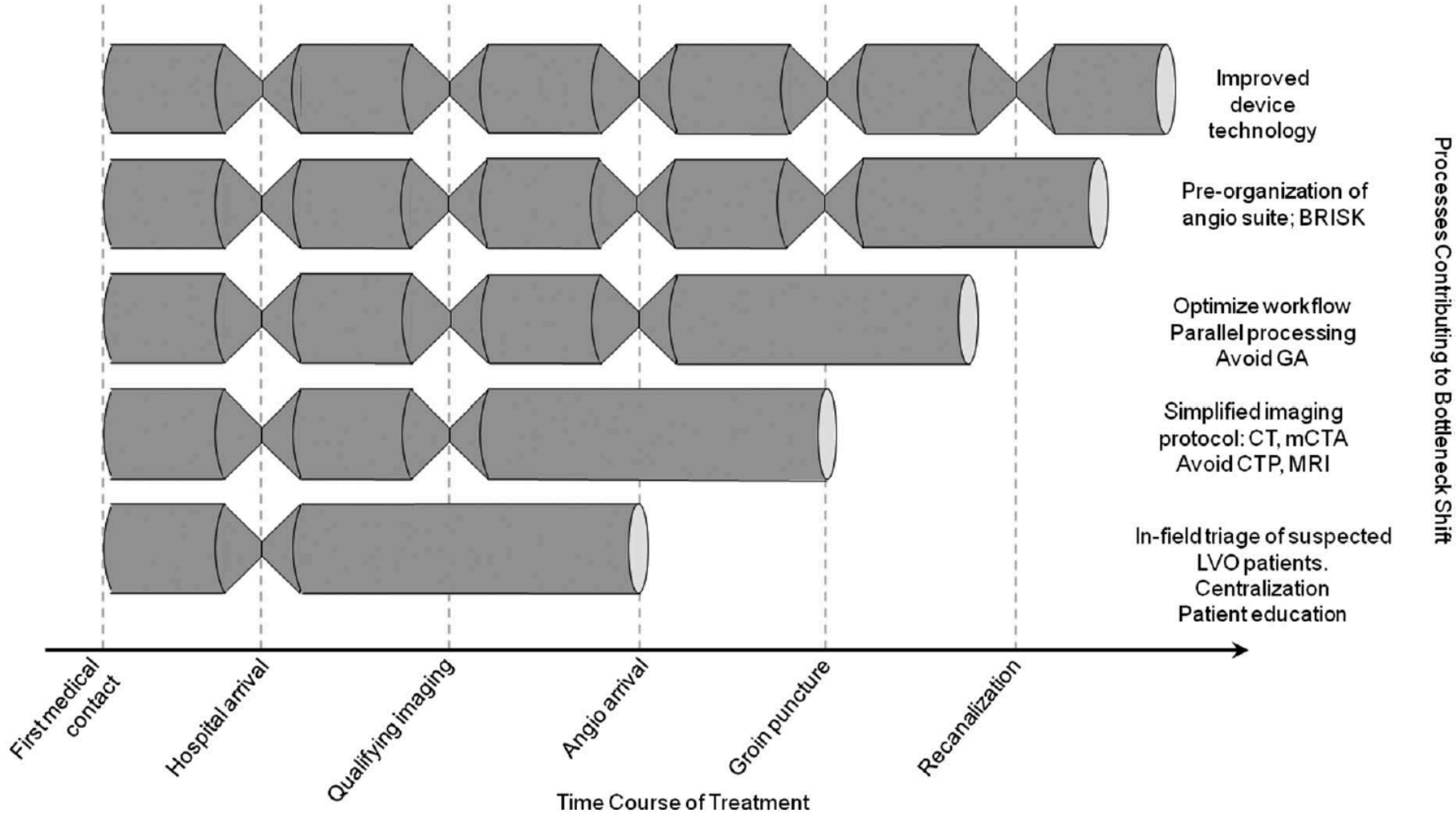
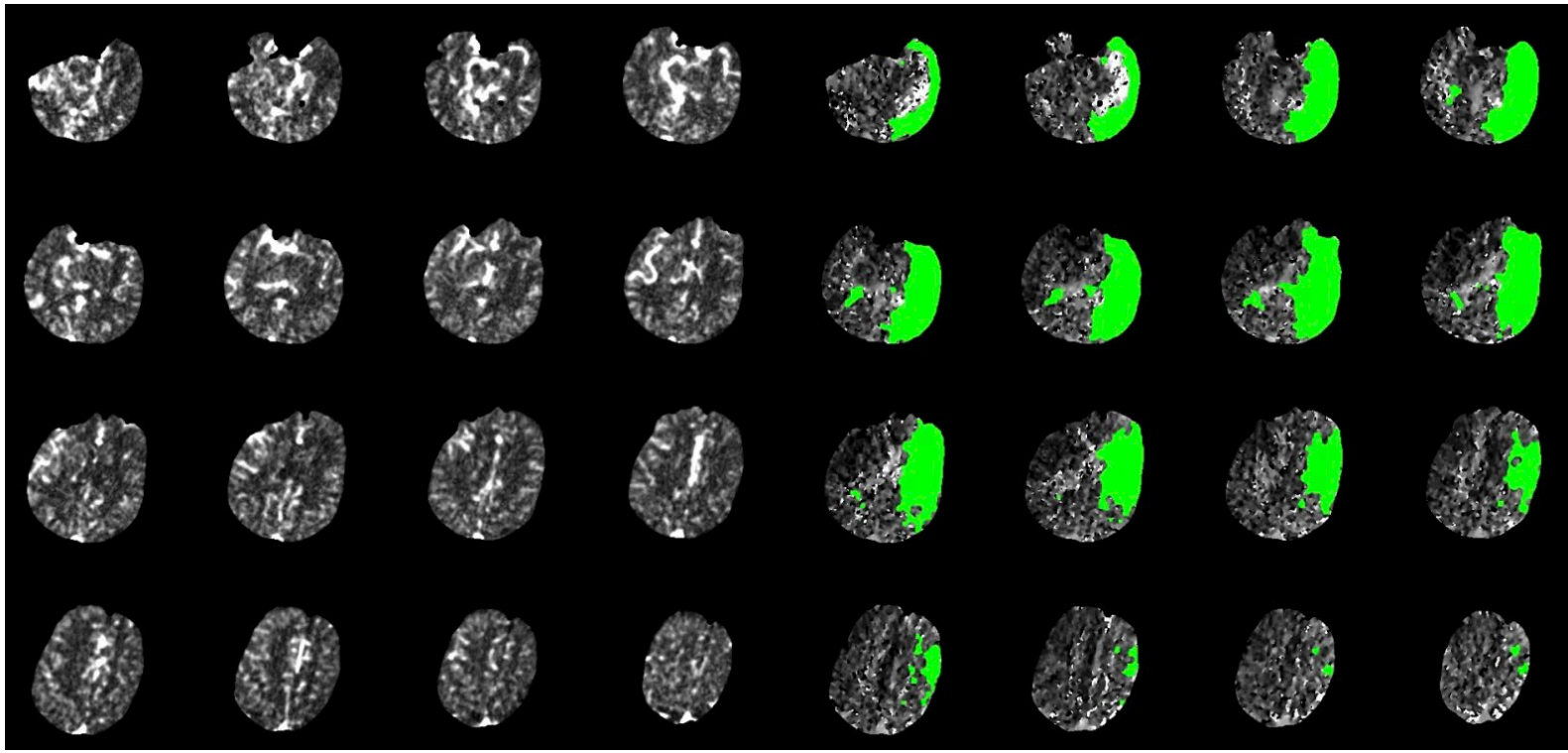


Figure 1 Shifting bottlenecks: the individual steps from first medical contact to final recanalization. Each pose potential rate-limiting steps in achieving fast reperfusion. Initial bottlenecks were faced in achieving fast recanalization and patient selection. With improvements at nearly every step, the remaining significant bottleneck is now in-field patient triage. BRISK, Brisk Recanalization Ischemic Stroke Kit; CTP, CT perfusion; GA, general anesthesia; LVO, large vessel occlusion.

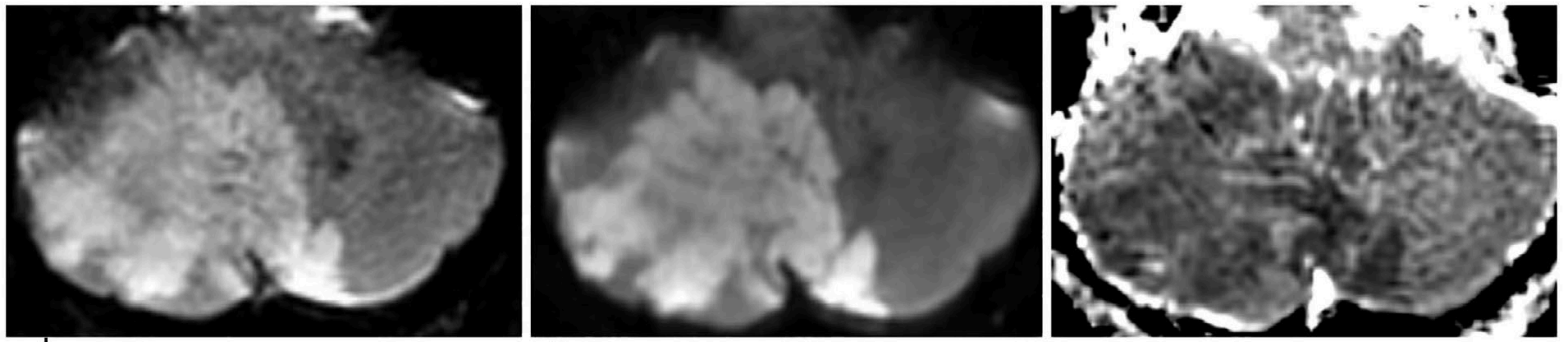
Goyal M et al. JNIS 2016

What Imaging Works Best for You?

- Direct-to-CT?
- CT/CTA?
- Perfusion (CT or MR)?
- Field-based imaging?
- Direct-to-MR?
- Direct-to-Angio?

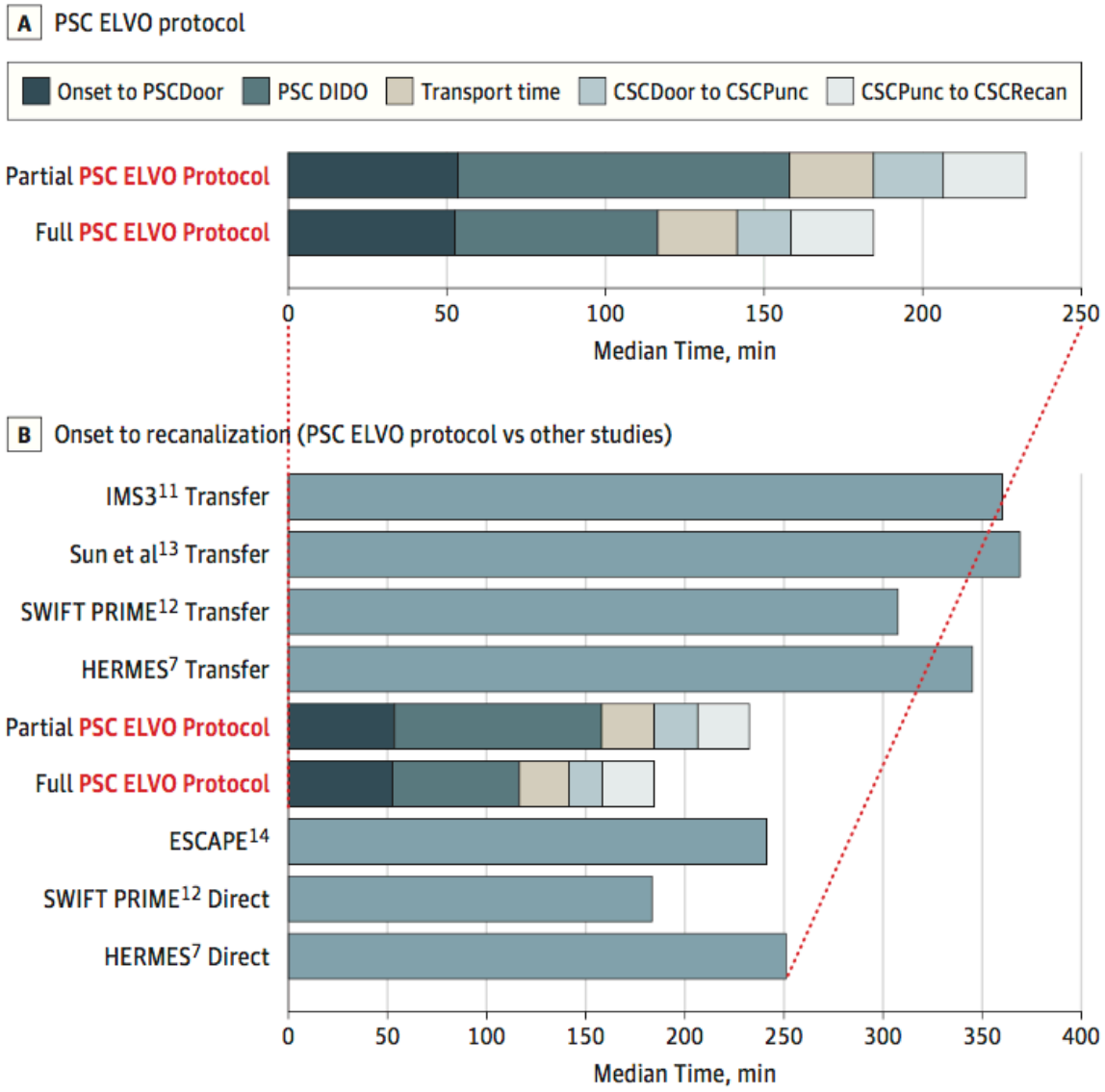


A 78 Seconds Complete Brain MRI Examination in Ischemic Stroke: A Prospective Cohort Study



Buren SA et al. J Magn Reson Imaging 2022

Figure 3. Primary Stroke Center (PSC) Emergent Large-Vessel Occlusion (ELVO) Protocol Care Efficiency Metrics



- **40 minute reduction in DIDO time (p<.001)**
- **Twice as likely to have a favorable outcome (50% vs. 25%, P<.04)**

McTaggart RA et al. JAMA Neurol 2017

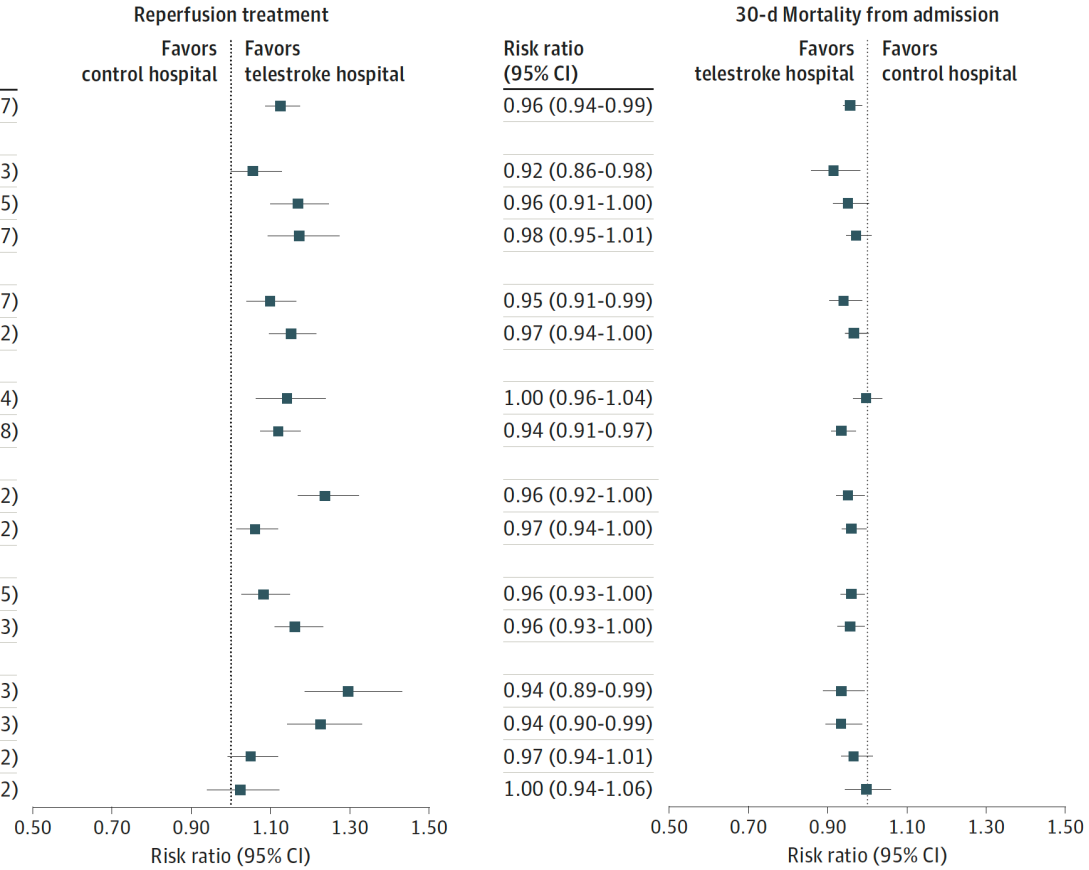
Reasons to Activate Neurology Expertise Early:

- ASRH designation states telemedicine “within 20 minutes of it being necessary”
- To assist is parallel-processing (review imaging, chart review for exclusion criteria to thrombolysis, patient examination and documentation)
- To confirm inclusion criteria for thrombolysis / thrombectomy
- To expedite interfacility transfer when necessary
- Earlier notification appears to streamline downstream processes

Reduce Barriers to Stroke Expertise

- **Among 153,272 stroke patients 2008-2017, those treated at telestroke hospitals were more likely to receive reperfusion treatment and had lower 30-day mortality**

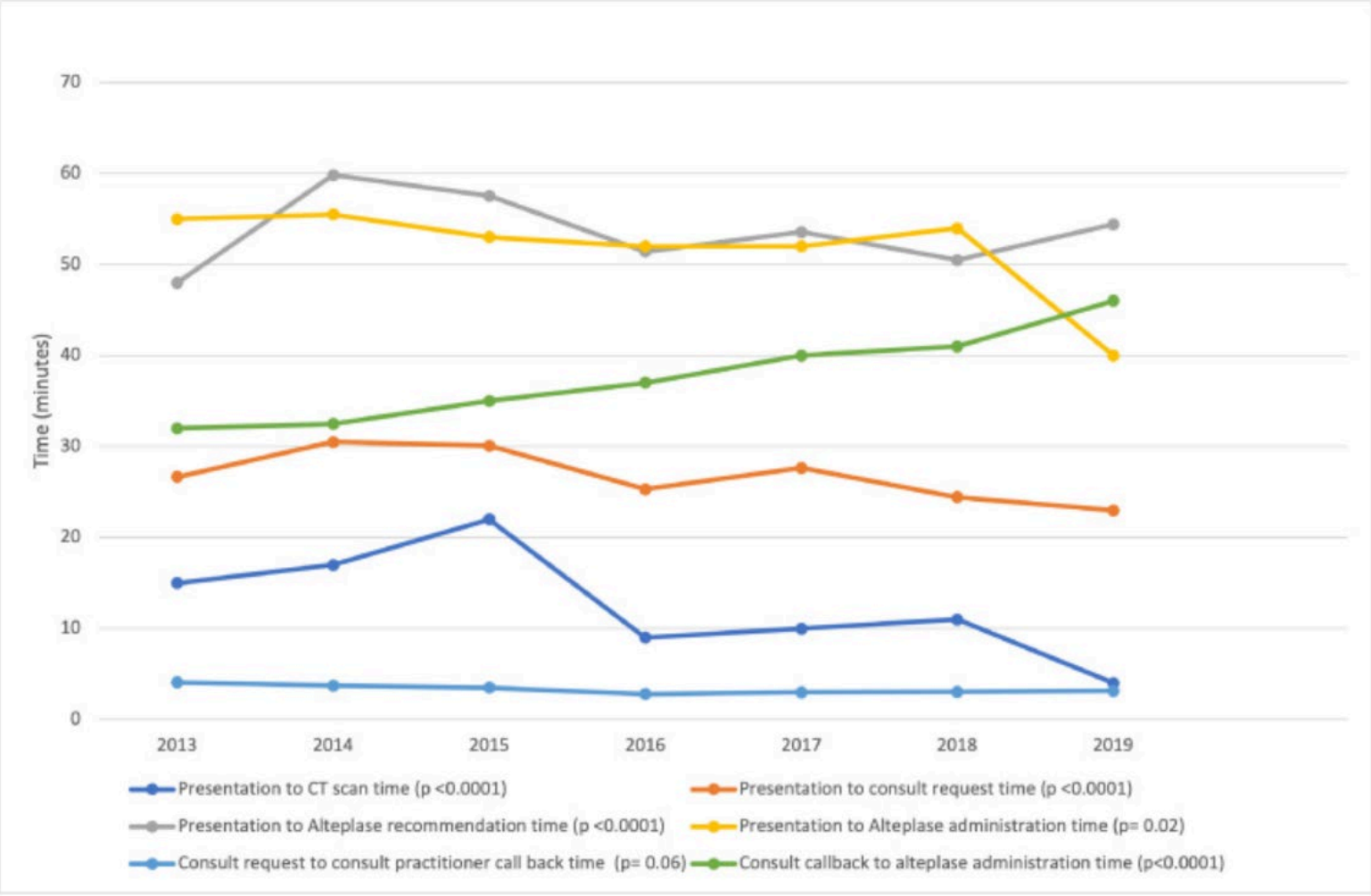
Subgroup	Patients, No.	Risk ratio (95% CI)	Risk ratio (95% CI)
Overall	153272	1.13 (1.09-1.17)	0.96 (0.94-0.99)
Age, y			
<75	52422	1.06 (1.00-1.13)	0.92 (0.86-0.98)
75-84	54102	1.17 (1.10-1.25)	0.96 (0.91-1.00)
≥85	46748	1.18 (1.09-1.27)	0.98 (0.95-1.01)
Sex			
Male	65154	1.10 (1.04-1.17)	0.95 (0.91-0.99)
Female	88118	1.15 (1.10-1.22)	0.97 (0.94-1.00)
History of atrial fibrillation			
Yes	35086	1.15 (1.06-1.24)	1.00 (0.96-1.04)
No	118186	1.12 (1.08-1.18)	0.94 (0.91-0.97)
Patient residence			
Rural	60012	1.24 (1.17-1.32)	0.96 (0.92-1.00)
Urban	93260	1.07 (1.02-1.12)	0.97 (0.94-1.00)
Thrombectomy era			
Before 2015	85600	1.09 (1.03-1.15)	0.96 (0.93-1.00)
2015 And after	67672	1.17 (1.11-1.23)	0.96 (0.93-1.00)
6-mo Hospital stroke volume			
1-11	27180	1.30 (1.19-1.43)	0.94 (0.89-0.99)
12-23	38480	1.23 (1.14-1.33)	0.94 (0.90-0.99)
24-52	58286	1.05 (0.99-1.12)	0.97 (0.94-1.01)
53-163	29326	1.03 (0.94-1.12)	1.00 (0.94-1.06)



Wilcock AD et al. JAMA Neurol 2021

Practice Makes Perfect

- **Among 67,736 telestroke calls at 132 sites between 2013-2019 – longer duration of participation was associated with shorter D2N times (39 min shorter per year, *p*=0.04)**



Zachrison KS et al. J Stroke and Cerebrovasc Dis 2021

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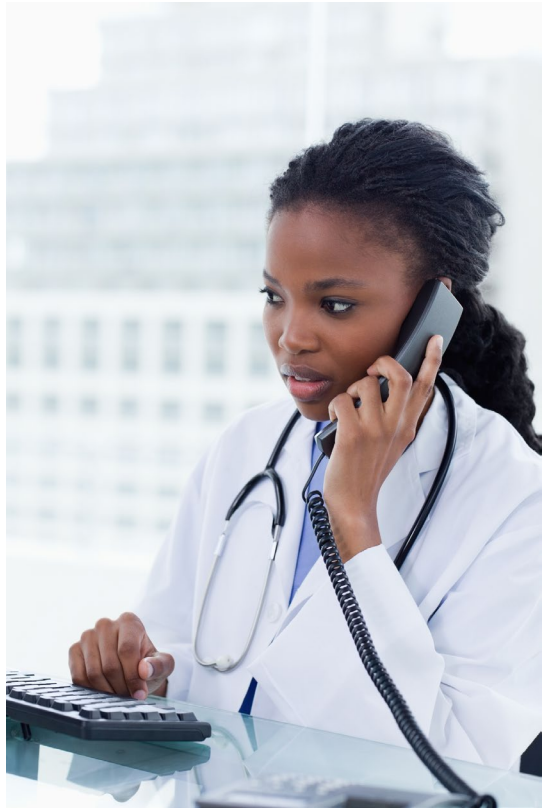
No Telestroke? – Keep it Simple

- Time LKW
- Description of ongoing deficits (NIHSS-ish)
- Blood glucose, vital signs
- Pertinent imaging findings
- Contraindications to thrombolysis



Summary of Current Contraindications to tPA
Nondisabling symptoms
Extensive/severe hypoattenuation on CT
Recent Ischemic stroke w/i 3 months
ICH on CT or hx of ICH/SAH
Acute head trauma (or severe w/i 3 months)
Intracranial/spinal surgery w/i 3 months
Coagulopathy (warfarin with INR>1.7, oral anticoagulant use w/i 48 hours or coag studies are normal, full dose heparin/LMWH within 24 hours). Do not generally wait for platelet count and coag studies, but do not administer if platelet count is known to be <100,000/mm^3, INR>1.7, aPTT>40s, or PT>15s
Current intracranial neoplasm, infective endocarditis, aortic arch dissection, GI malignancy
GI bleeding w/i 21 days

Powers WJ et al. Stroke 2019

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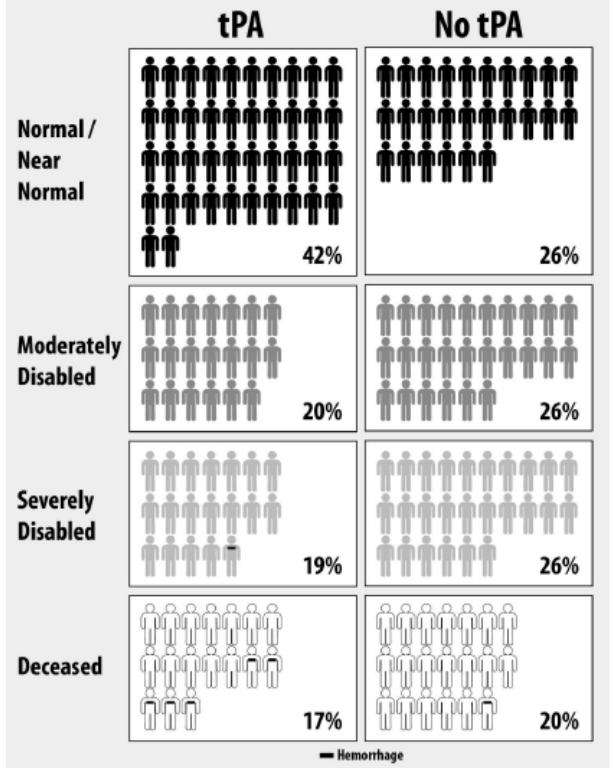
Discussing Risks & Benefits of tPA

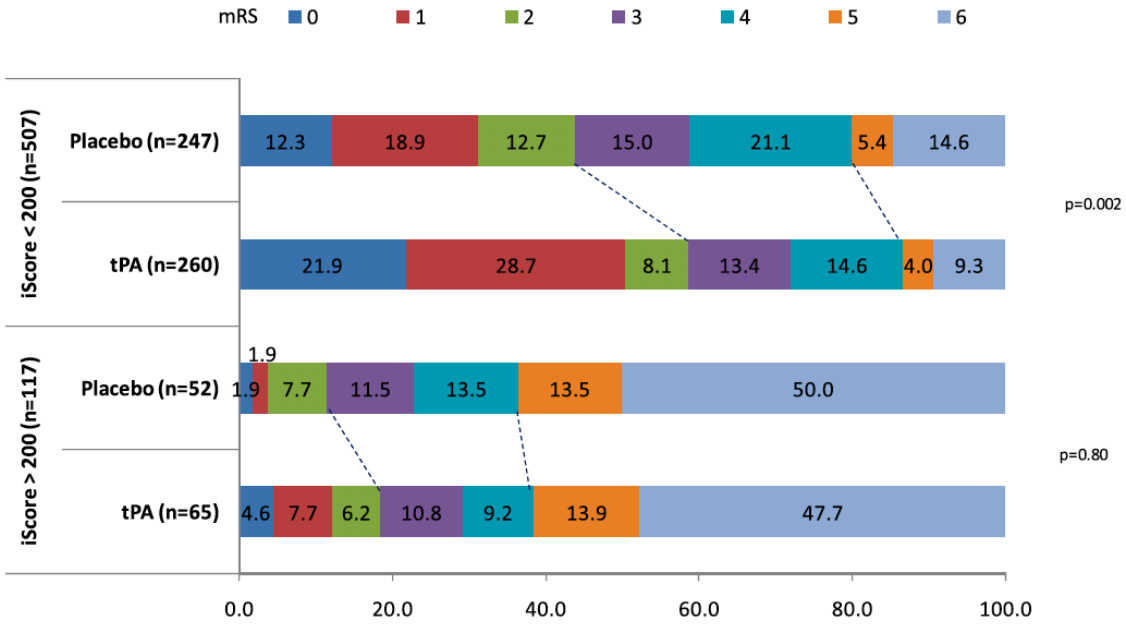
- **Opportunity for consensus language that conveys an institutional standard rather than placing pressure on providers in the moment**
- **This shows the 3 month outcomes of 100 patients treated within 3 hours of stroke onset:**
  - **Patients treated with tPA are between 1.5 and 2x as likely to return to normal or near normal function at 3 months**
  - **1 in 7 patients who receive tPA have an improvement in outcome due to the drug**
  - **The effects of the drug are time-dependent. If the drug can be given within 1.5 hours of onset, the chance of improvement increases to 1 in 3**
  - **1 in 18 patients who received tPA had significant bleeding due to the drug**
  - **The risk of dying from the stroke is similar regardless of the treatment**
  - **tPA increases the chances of functional independence, but with a 10-fold increase in risk of bleeding**



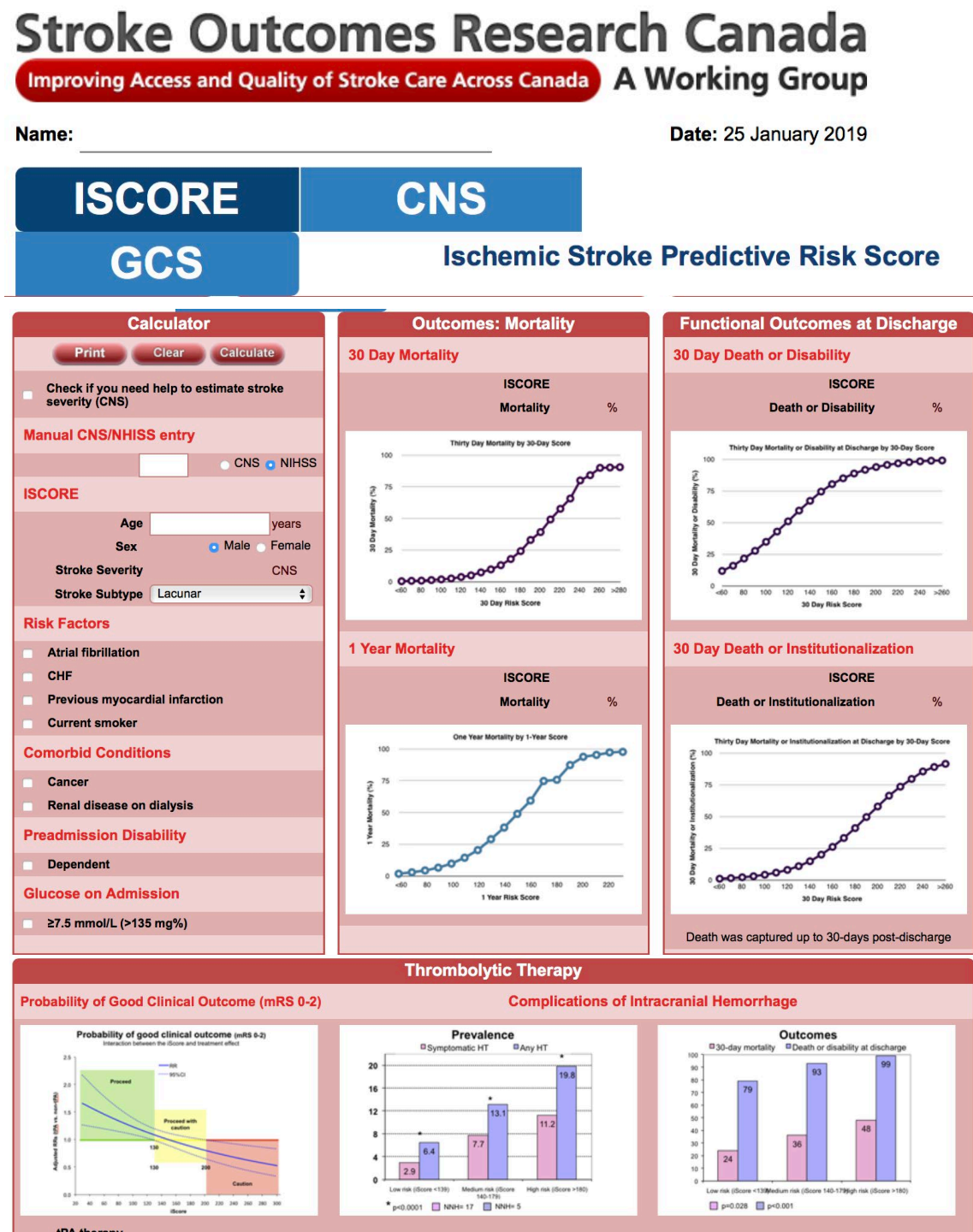
Gadhai et al. Stroke 2010

Can we better predict individual clinical response to thrombolysis?

- iScore applied to >12,000 patients at 154 sites
- iScore ≥ 200: NNT 385, NNH 5-17; p<0.05
- Validated in NINDS cohort:



Saposnik G et al. J Stroke Cerebrovasc Dis 2013



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Ensuring Diagnostic Accuracy

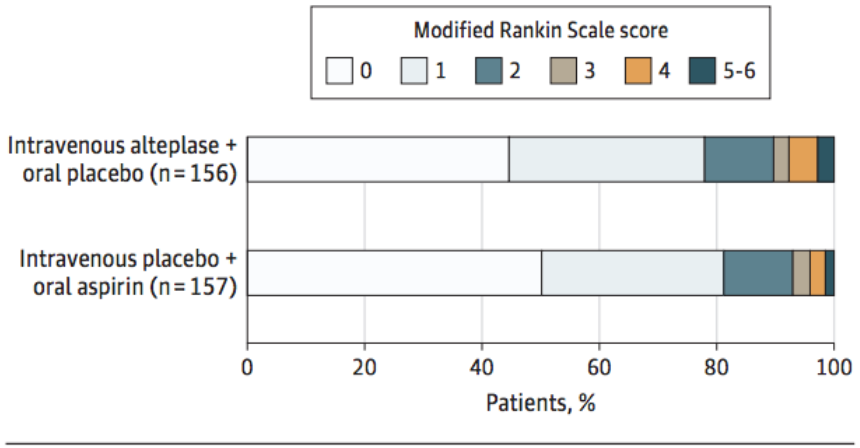
- **Prioritize assessment to measuring ongoing focal neurologic deficits:**
  - **Negative symptoms suggest ablative phenomena – i.e stroke**
  - **Positive symptoms suggest irritative / non-ischemic phenomena**
- **When tPA is given to a stroke mimic, complications are rare:**
  - **Among a cohort of 72,582 tPA treated patients from 2010-2017:**
    - **sICH 0.4% (aOR 0.29; 95% CI, 0.17-0.50) vs. 3.5% in stroke**
    - **In-hospital mortality 0.8% (aOR 0.31; 95% CI, 0.20-0.49) vs. 6.2% in stroke**

	Stroke Mimics N=2517	Ischemic Stroke N=70 065	Adjusted OR (95% CI)	*P* Value
Safety end points				
Symptomatic intracranial hemorrhage	11 (0.4)	2451 (3.5)	0.29 (0.17–0.50)	<0.001
Life-threatening or serious systemic hemorrhage	1 (0)	516 (0.7)	0.15 (0.03–0.84)	0.03
Other serious complication	26 (1.0)	1938 (2.8)	0.73 (0.51–1.03)	0.08
Any tPA complication*	38 (1.5)	4803 (6.9)	0.48 (0.36–0.64)	<0.001

Ali-Ahmed F et al. Circulation: Cardiovasc Qual and Outcomes 2019

Should tPA be Used in Minor Nondisabling Stroke?

- PRISMS trial terminated after 313/948 enrolled
- NIHSS 0-5 AND deficits "not clearly disabling"
- No significant difference in mRS 0-1 at 90 days
- sICH 3.2% vs. 0% (risk diff, 3.3%, 95%CI 0.8-7.4)



Khatri P et al. JAMA 2018

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)

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Be Vigilant for Deterioration or Complication

Table 6. Management of Symptomatic Intracranial Bleeding Occurring Within 24 Hours After Administration of IV Alteplase for Treatment of AIS

COR IIb	LOE C-EO
Stop alteplase infusion	
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match	
Emergent nonenhanced head CT	
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL	
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)	
Hematology and neurosurgery consultations	
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control	

AIS indicates acute ischemic stroke; aPTT, activated partial thromboplastin time; BP, blood pressure; CBC, complete blood count; COR, class of recommendation; CPP, cerebral perfusion pressure; CT, computed tomography; ICP, intracranial pressure; INR, international normalized ratio; IV, intravenous; LOE, Level of Evidence; MAP, mean arterial pressure; and PT, prothrombin time.

Sources: Sloan et al,[138] Mahaffey et al,[139] Goldstein et al,[140] French et al,[141] Yaghi et al,[142–144] Stone et al,[145] and Frontera et al.[146]

Table 7. Management of Orolingual Angioedema Associated With IV Alteplase Administration for AIS

COR IIb	LOE C-EO
Maintain airway	
Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.	
Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation.	
Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis after IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.	
Discontinue IV alteplase infusion and hold ACE inhibitors	
Administer IV methylprednisolone 125 mg	
Administer IV diphenhydramine 50 mg	
Administer ranitidine 50 mg IV or famotidine 20 mg IV	
If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL	
Icatibant, a selective bradykinin B_2 receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed a total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACE inhibitor-related angioedema	
Supportive care	

ACE indicates angiotensin-converting enzyme; AIS, acute ischemic stroke; COR, class of recommendation; IV, intravenous; and LOE, Level of Evidence.

Sources: Foster-Goldman and McCarthy,[147] Gorski and Schmidt,[148] Lewis,[149] Lin et al,[150] Correia et al,[151] O'Carroll and Aguilar,[152] Myslimi et al,[153] and Pahs et al.[154]

- Intra- and post tPA monitoring is time intensive!
  - Serial neurologic assessments and vital signs every 15 min for 2 hours, then every 30 min for 6 hours, then hourly until 24 hours post tPA
- Have a readily accessible protocol for sICH and orolingual edema

Powers WJ et al. Stroke 2019

Ensure Appropriate Disposition

- **Organized stroke unit care is associated with improved outcomes (OR 0.77; 95% CI, 0.69-0.87)**
- **If no dedicated stroke unit, be sure to do the basics well:**
  - **Control fever, blood glucose and aspiration risk**

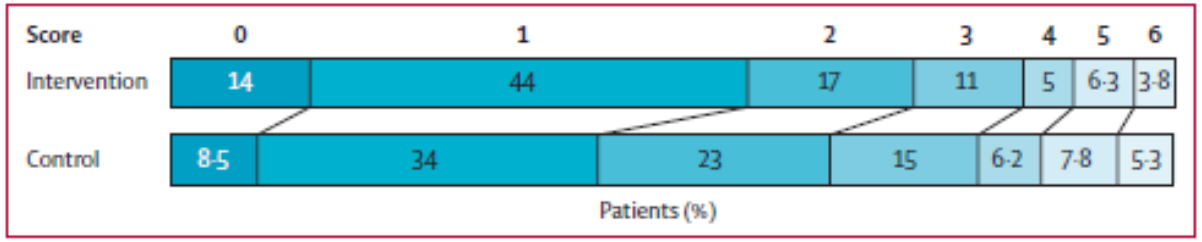

Figure 3: Distribution of 90-day modified Rankin scale*
*Percentages may not total to 100% due to rounding.

- **NNT 6.4 to prevent death or significant disability at 90 days**

Langhorne P et al. Cochrane Database Syst Rev 2020
Middleton S et al. Lancet Neurol 2011

Keep the Wheels Greased

- Education, simulation & feedback are critical at low volume centers
- Focusing on OTT and DIDO ensures stakeholders are mindful to the entire stroke chain of survival
- For many resource-limited settings EMS holds the key to efficiency on the front & back end

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Strategies to streamline interfacility transfers

- Hold EMS when transfer suspected prior to arrival
- Auto accept at regional hub
- Consider 'give and go' instead of 'drip and ship'
  - Tenecteplase appears to be non-inferior to alteplase and has been shown to reduce D2N and DIDO times
  - Bolus only dose over 5-10 seconds

	Entire Sample			Class 1 Subgroup		
	ALT (n=354)	TNK (n=234)	*P* value	ALT (n=219)	TNK (n=143)	*P* value
Door-in-door-out (DIDO)						
Minutes	135 (100, 177) n = 65	113 (83, 153) n=43	.054	126 (98, 167) n=32	88 (83, 182) n=9	.3
within 90 min	9 (14%)	16 (37%)	**.010**	4 (12%)	5 (56%)	**.014**
Needle to door out time						
Minutes	58 (32,108) n= 67	42 (28, 74) n=43	.13	61 (37, 112) n=33	42 (36, 121) n=9	.5
within 60 minutes	34/65 (52%)	29 (67%)	.2	16/32 (50%)	6 (67%)	.5

Warach SJ et al. 2022 [preprint] https://doi.org/10.1101/2022.07.12.22277564

Take Home Points

- Exceptional ED stroke care is achievable in resource-limited settings
- Requires alignment of the system-of-care including prehospital severity grading and destination protocols
- Align early ED priorities to streamline time to diagnosis when a reperfusion decision is to be made
- Involve neurologic expertise by telemedicine or phone early
- Be mindful of the impact of DIDO and downstream efficiency on optimizing patient outcomes

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