Optimizing Regional Systems of Care: Lessons from the Nation's Most Populous County

Jeffrey L. Saver, MD

SA Vice-Chair and Professor of Neurology

Director, UCLA Comprehensive Stroke and Vascular Neurology Program

JLS Disclosures

- Unpaid site investigator in multicenter trials run by Medtronic, Stryker, Cerenovus, and Rapid Medical for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled.
- Receives funding for services as a scientific consultant regarding trial design and conduct to Medtronic, Stryker, Cerenovus, BrainsGate, Rapid Medical, Boehringer Ingelheim (prevention only), and Abbott.
- Serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr. Saver received any payments for this voluntary service
- Employee of the University of California. The University of California has patent rights in retrieval devices for stroke.

Los Angeles

UCLA Stroke Center

Population and Resources

UCLA Stroke Center

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Los Angeles County

- 10.1 million individuals
- 4,751 sq miles
- 31 EMS agencies
  - » 161 ambulances, 1 MSU
  - » Paramedic responders
- 52 designated stroke centers
  - » 16 CSC, 4 TSC, 30 PSC

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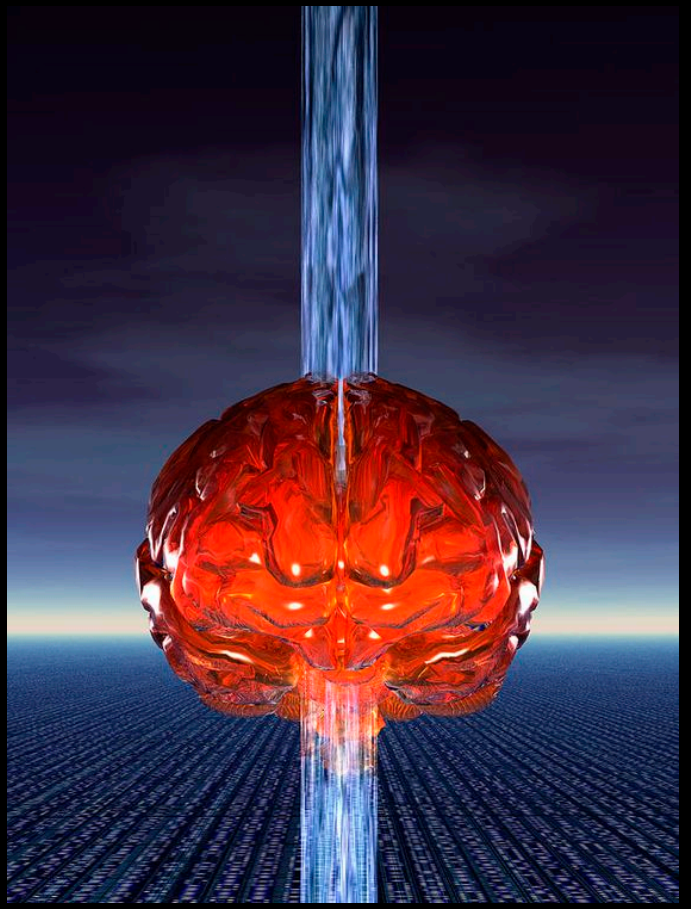
State of Massachusetts

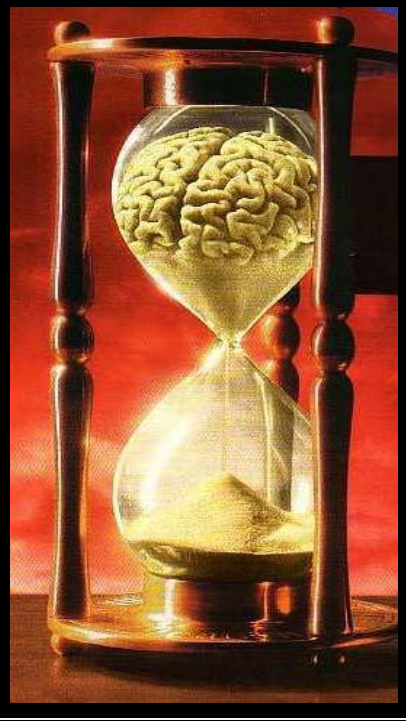
- 6.4 million individuals
- 10,550 sq miles
- 322 EMS agencies
  - » Lots of ambulances
  - » Paramedic/EMT responders
- 68 designated stroke centers
  - » 68 PSC

Talk Outline

- Stroke from the perspective of EMS Regional Systems of Stroke Care
  - » Types of stroke
  - » Types of emergency stroke treatments
  - » Types of emergency stroke centers
- Time is Brain
- Building Efficient Prehospital Care Systems
  - » Calling 911
  - » Dispatch
  - » Prehosptial care
    - Standard Ambulances – Paramedics/EMTs
      - » Stroke recognition
      - » LVO recognition
      - » Routing
      - » Neuroprotection
    - Mobile Stroke Units
- Future directions



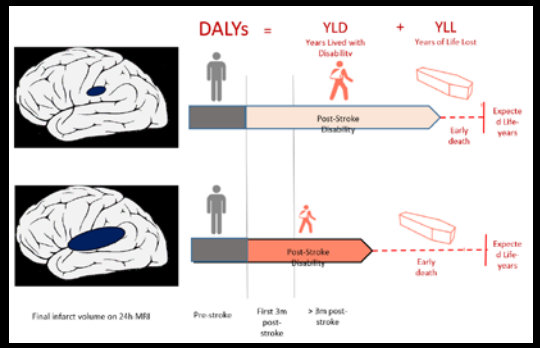
Time is Brain



2 million neurons per minute

--Saver, Stroke 2006
--Saver, Brain 2017

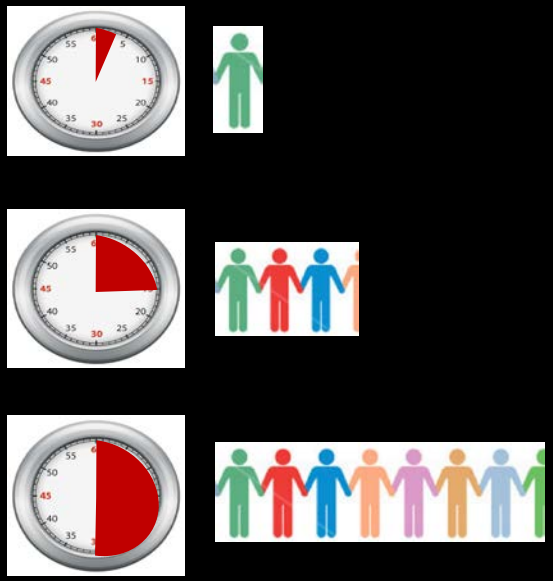
Brain is Life



1 drop of brain, 1 week of life

--Kawano et al, Brain 2017
--Saver et al, JAMA 2017

Time is Patients

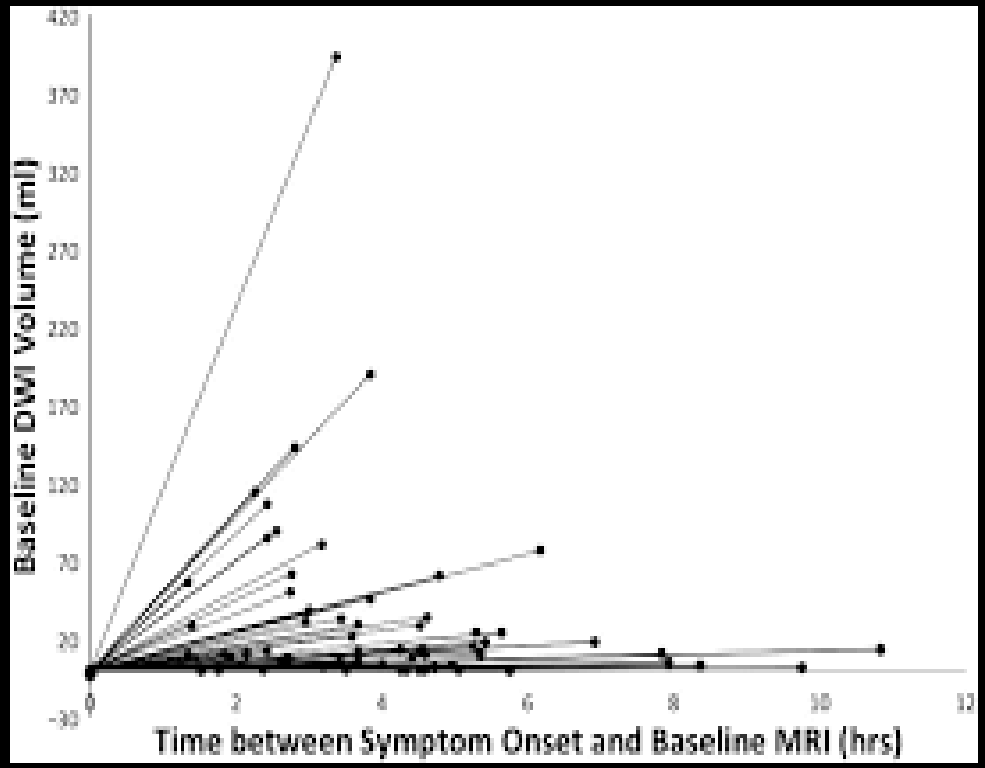


1 worse outcome every 4 minutes

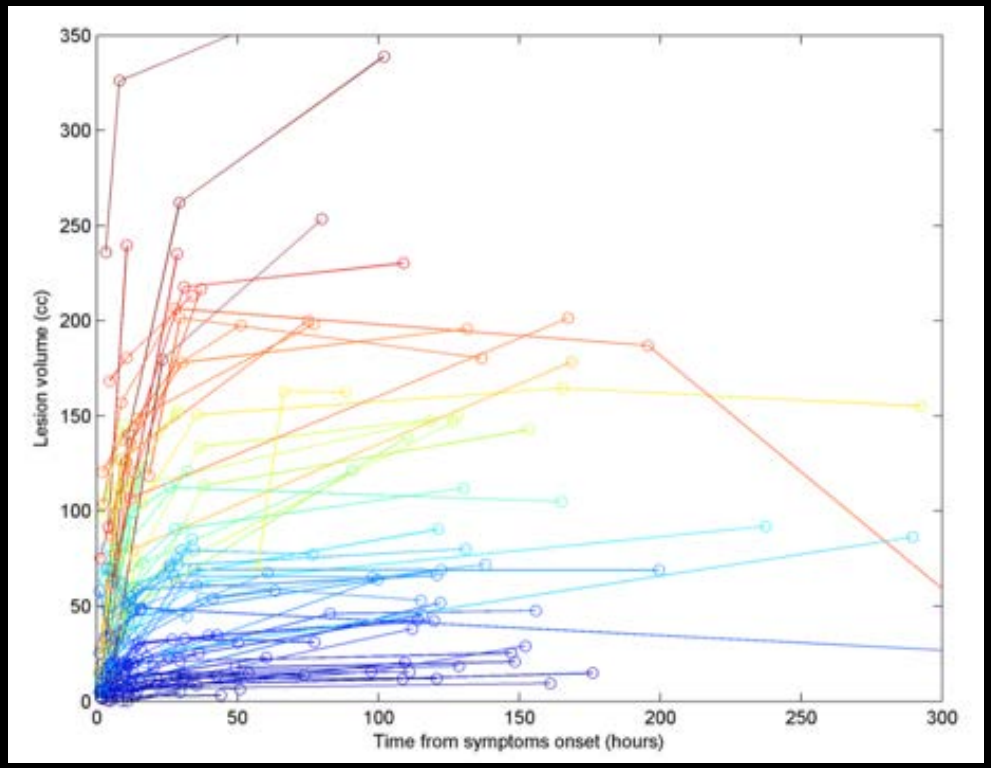
Time is Life

Save 1 min, save 1 week of life*

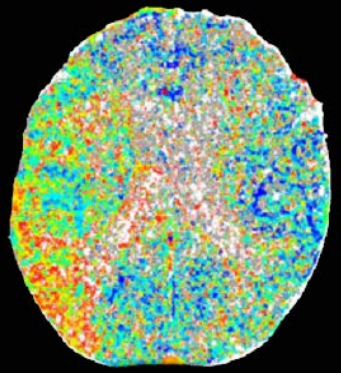
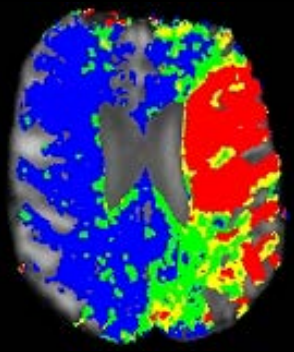
Progressors: Fast / Slow / Variable



DEFUSE 2
--Wheeler et al, Int J Stroke 2015



UCLA Series
--Liebeskind, 2016

	Tissue Status	Perfusion Status	Vessel Status
Multimodal CT	**CBV CT** 	**PCT** 	**CTA** 
Multimodal MRI	**DWI** 	**PWI** 	**MRA** 
	Bioenergetic Compromise	Hemodynamic Compromise	Occlusions or Stenoses

Strategies to Identify LVO Patients with Salvageable Ischemic Penumbra

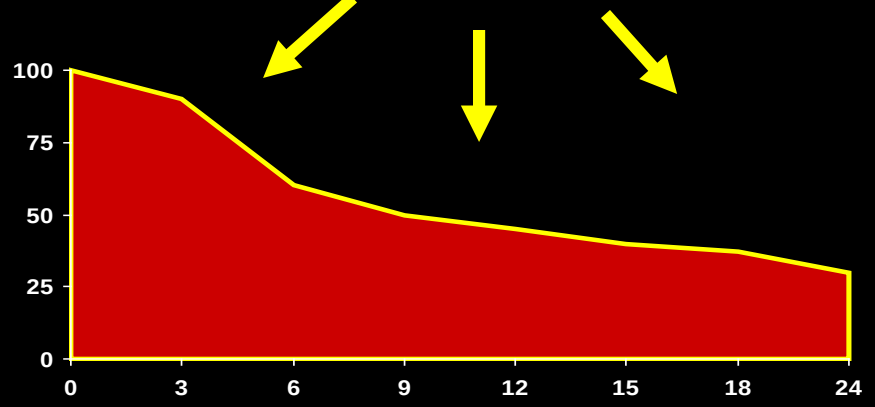
< 6 Hrs

=

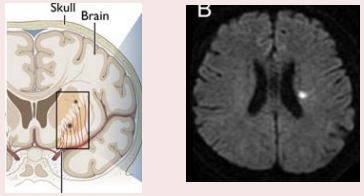
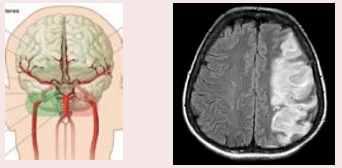
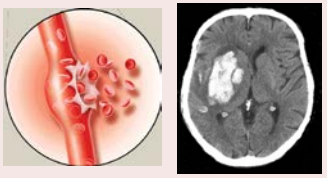
Hyperacute therapy when nearly all patients have penumbra

> 6 Hrs

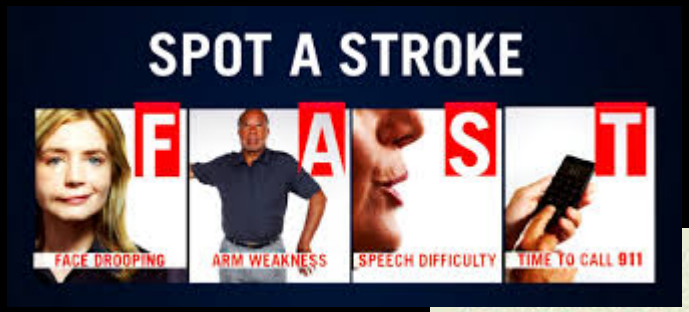
Imaging required to assess pathophysiology



Major Stroke Subtypes: A Prehospital Perspective

	Ischemic		Hemorrhagic	
	Small/Medium Vessel Occlusoin	Large Vessel Occlusion	Intraparenchymal	Subarachnoid
				
Typical Presentation	Focal Deficits	Focal Deficits	Focal Deficits	Non-Focal Deficits
Major Treatments	1) ≤4.5h: IV TPA 2) >4.5-12h: IV TPA in imaging-selected subset	1) ≤4.5h: IV TPA plus ET 2) ≤ 6h: ET 3) 6-24h: ET in imaging-selected subset	1) Anticoag reversal 2) BP moderation 3) Ventriculostomy 4) Surgical evac	1) Coiling/ clipping 2) NICU vasospasm management
Population Freq of Focal	65%	35%	10%	N/A
EMS Freq of Forcal	40%	35%	25%	N/A

Warning Signs and Activation of EMS System



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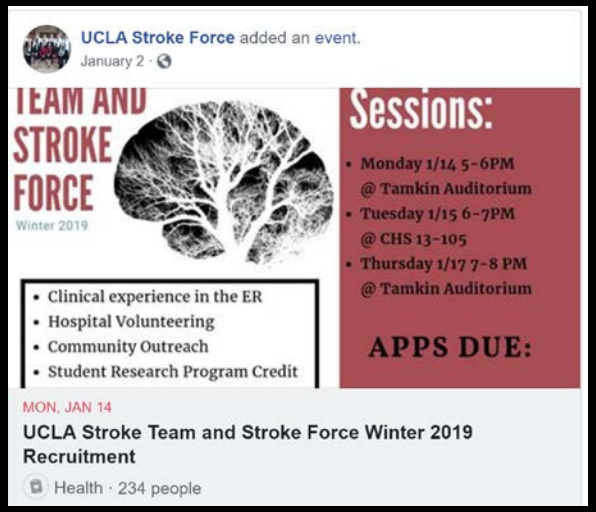
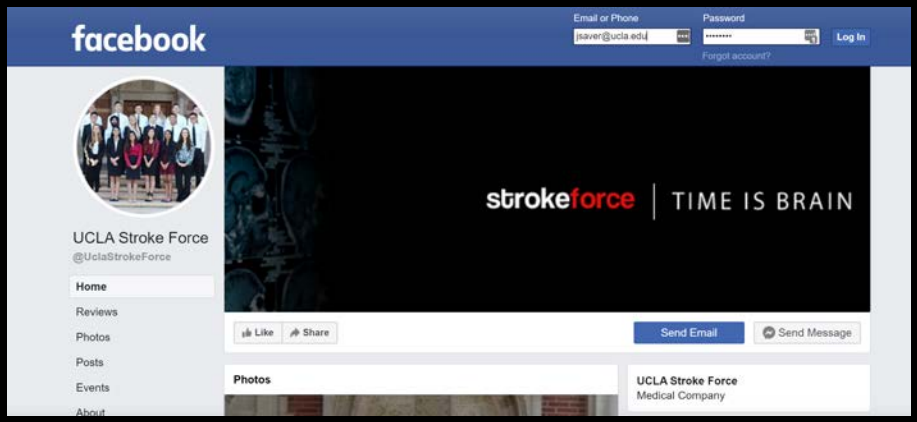
UCLA Stroke Force and StrokeTeam

>107 languages spoken in LA





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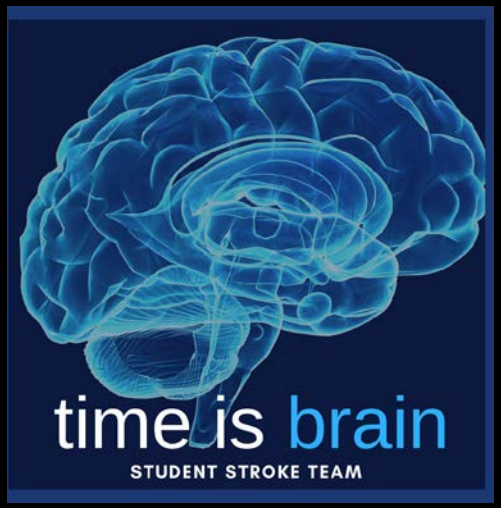


Who To Activate EMS for?

Ubiquitous Monitoring and Ambient Intelligence

Accelerated Stroke Onset Detection

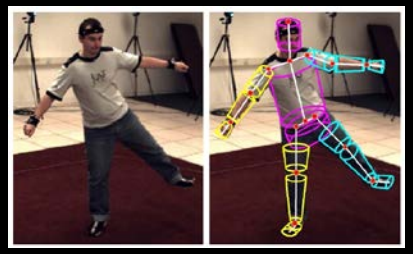
Las Vegas Casinos

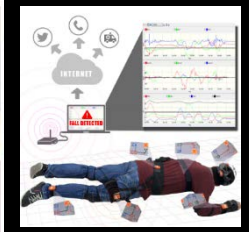
Home Cameras/Voice Assistants

Home Health Robots

Smart Phones

Acclerometer and Computer Vision - Fall Detection





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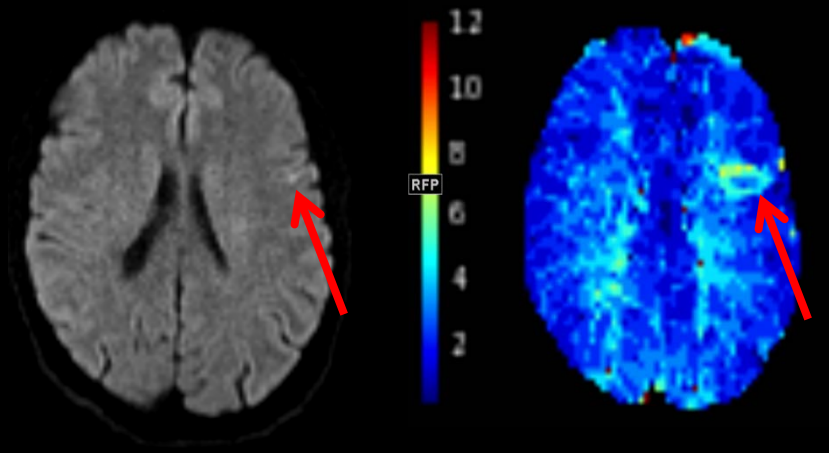
--Example: Leone et al. Detecting falls with 3d range camera in ambient assisted living applications. Medical Engineering & Physics 2011

Altered Speech Detection by AI Voice Assistants

- 47 yo man wakes to Alexa alarm
- Voice assistant initially does not understand dysarthic, mildly dysfluent commands to turn alarm off
- Proceeds to read and send texts on iphone
  - » But speech still slurred
  - » Slight right facial
- Diffusion and Tmax small lesion left frontal operculum



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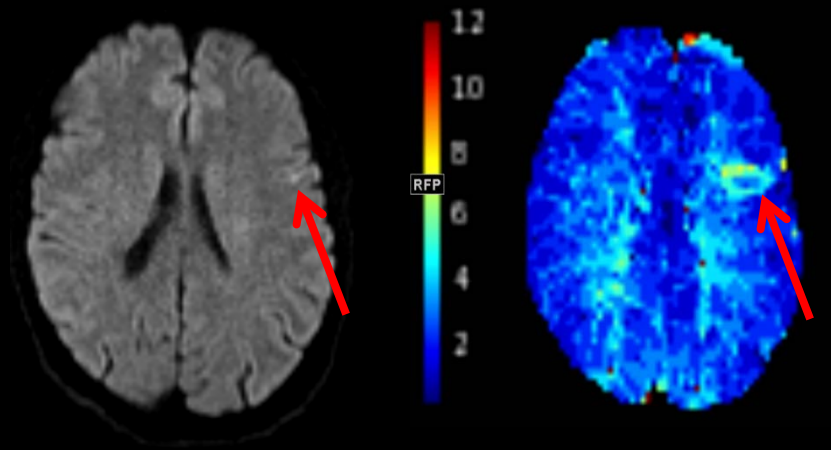
aAlexa without agraphia



Stroke and EMS

- Narrow therapeutic time window
- Early intervention critical for stroke care
- Prehospital personnel
  - » 35-70% of stroke patients arrive by ambulance
  - » Unique position: first medical professional to come in contact with stroke patient

Goal of EMS Dispatch

- To send the right things to the right people at the right time in the right way and to do the right thing until help arrives

Dispatch and Stroke

- Enhanced 911 systems automatically display caller's address
  - » Especially helpful for dysarthric/aphasic patients
- Dispatcher assesses complaint and determines
  - » Dispatch priority
  - » Level of expertise (ALS or BLS)
- Structured algorithms for caller interaction
  - » National Academy Medical Priority Dispatch System QA Dispatcher Guide
    - Protocols for 36 chief complaints, including stroke (28)

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Prehospital Paramedic Stroke Recognition and Characterization: Applications

- Rapid prehospital care
  - » “Scoop and go”
- One-tier Stroke Center systems
  - » Route directly to designated Stroke Centers
  - » Pre- arrival notification
    - Activate stroke team
    - Clear head CT/MR scanner
    - Preregister and issue temporary medical record number
  - » Direct to CT/MR transport
- Two-tier Stroke Center systems
  - » Selective direct transport to Comprehensive Stroke Centers
- Treatment in the field
  - » Paramedic
    - Neuroprotectives
    - BP moderation
  - » Physician
    - Thrombolysis

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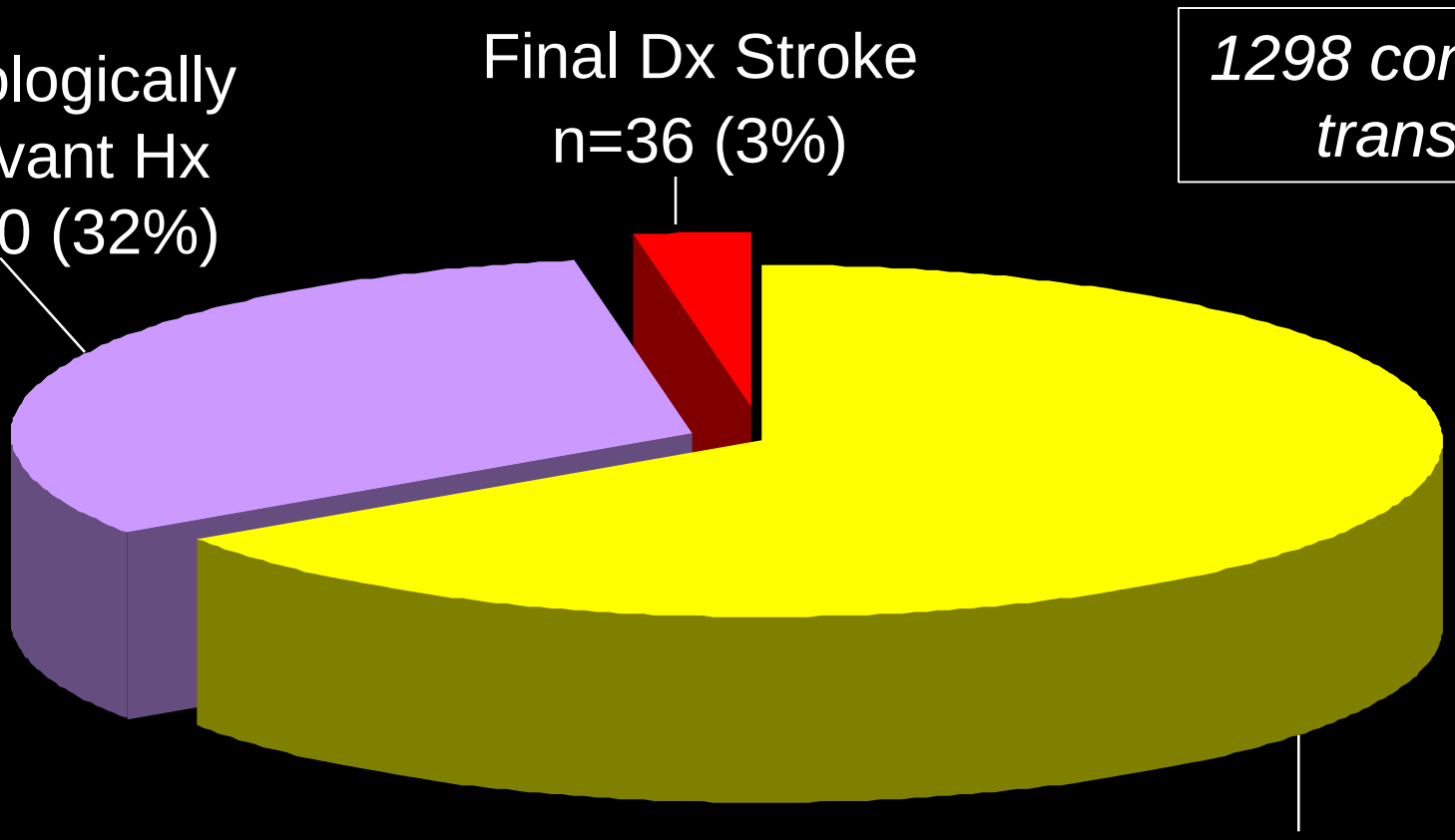
Strokes Are Only 2-3% of Prehospital Transports

1298 consecutive transports



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--Stroke 2000;31:71-6

“Stroke Recognition” Tools

Stroke vs Non-Stroke

- Los Angeles Prehospital Stroke Screen (LAPSS)* **
- Cincinnati Prehospital Stroke Scale (CPSS)*
- Face Arm Speech Test**
- Paramedic Quick Screen (San Diego)
- Miami Evaluation of Neurologic Deficit (MEND)
- UAB Stroke Observational Scale (SOS)
- Expanded LAPSS (Melbourne Acute Stroke Screen) **
- …

“Stroke Severity” Tools

LVO vs Non-LVO Stroke

CSC Approp (LVO+ICH) vs not

- Los Angeles Motor Scale (LAMS)
- 3 Item Stroke Scale (3I-SS)
- Rapid Arterial OcClusion Evaluation Score (RACE)
- Cincinnati Prehospital Stroke Severity Scale (CPSSS)
- Field Assessment Stroke Triage for Emergency Destination (Fast-ED)
- Vision, Aphasia, Neglect (VAN)
- …

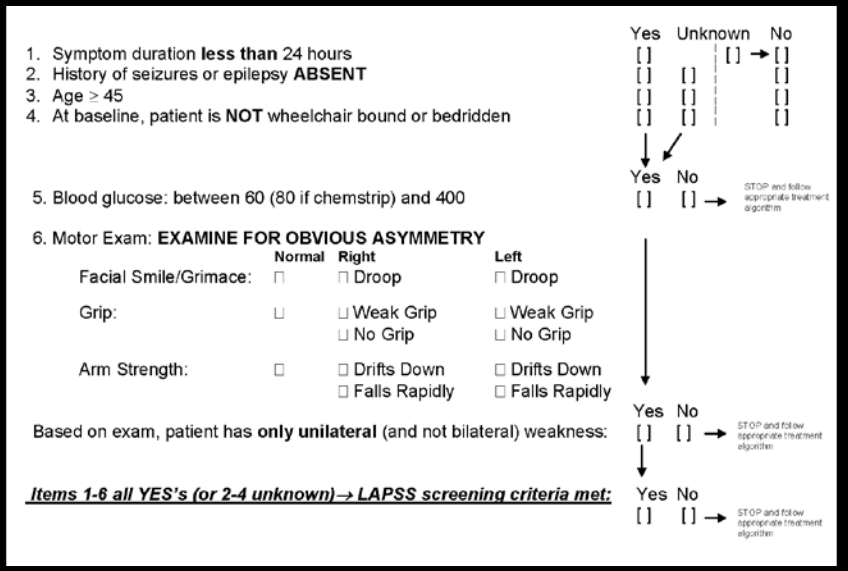
*Endorsed in ACLS Cardiopulmonary Resuscitation Guidelines, Circulation 2010

**Prospectively validated in field testing

LAPSS

Los Angeles Prehospital Stroke Screen

- History (4 items)
  - » onset/duration of symptoms
  - » age
  - » history of seizure disorder
  - » baseline functional status
- Exam (3 items): identifies unilateral weakness
  - » facial weakness
  - » arm drift
  - » grip strength
- Fingerstick blood glucose (1 item)



	Yes	Unknown	No
1. Symptom duration **less than** 24 hours	[ ]	[ ] →	[ ]
2. History of seizures or epilepsy **ABSENT**	[ ]	[ ]	[ ]
3. Age ≥ 45	[ ]	[ ]	[ ]
4. At baseline, patient is **NOT** wheelchair bound or bedridden	[ ]	[ ]	[ ]

	Yes	No
5. Blood glucose: between 60 (80 if chemstrip) and 400	[ ]	[ ] → STOP and follow appropriate treatment algorithm

6. Motor Exam: **EXAMINE FOR OBVIOUS ASYMMETRY**

	Normal	Right	Left
Facial Smile/Grimace:	☐	☐ Droop	☐ Droop
Grip:	☐	☐ Weak Grip ☐ No Grip	☐ Weak Grip ☐ No Grip
Arm Strength:	☐	☐ Drifts Down ☐ Falls Rapidly	☐ Drifts Down ☐ Falls Rapidly

	Yes	No
Based on exam, patient has **only unilateral** (and not bilateral) weakness:	[ ]	[ ] → STOP and follow appropriate treatment algorithm
Items 1-6 all YES's (or 2-4 unknown)→ LAPSS screening criteria met:	[ ]	[ ] → STOP and follow appropriate treatment algorithm

Cincinnati Prehospital Stroke Scale

Facial Droop

Normal: Both sides of face move equally
Abnormal: One side of face does not move at all

Arm Drift

Normal: Both arms move equally or not at all
Abnormal: One arm drifts compared to the other

Speech

Normal: Patient uses correct words with no slurring
Abnormal: Slurred or inappropriate words or mute

Motor Deficits in Acute Stroke

- LAPSS and CPSS emphasize motor deficits:
  - » Present in 83-90% of all strokes
  - » Major determinant of long-term disability
  - » Testing performed reliably and briefly by health personnel not specifically trained in neurology

LAPSS: Prospective Field Performance

LAPSS Completed Runs (Neuro Sx Runs)

Sensitivity	91% (76-98%)
Specificity	99% (97-99%)
Positive Predictive Value	97% (84-99%)
Negative Predictive Value	98% (96-99%)

--Stroke 2000;31:71-6

Prehospital Stroke Management

- Perform
  - » Determine and document time of onset
  - » Initiate cardiac monitoring
  - » Insert intravenous line
  - » Perform serum glucose measure
  - » Administer oxygen
  - » Notify ED quickly
  - » Transport as soon as possible (“scoop and go”)

- Avoid
  - » Delay transport
  - » Give large volumes of fluid
  - » Give dextrose (unless hypoglycemic)

Regional Stroke Systems of Care: Four Tier US Model

- **EMS**
  - --Trained dispatchers, high priority triage
  - --Paramedics trained in stroke recognition (e.g. LAPSS)
  - --Deliver patients to nearest stroke capable hospital
  - --Pre-arrival notification

- **Spokes**
  - **Acute Stroke Ready Hospitals**
    - --Able to provide initial, ED care, often via telemedicine
    - --Able to use rt-PA and other acute therapies safely and efficiently
  - **Primary Stroke Centers**
    - --Able to provide initial, ED care
    - --Able to use rt-PA and other acute therapies in a safe and efficient manner
    - --Have Stroke Units and can admit patients

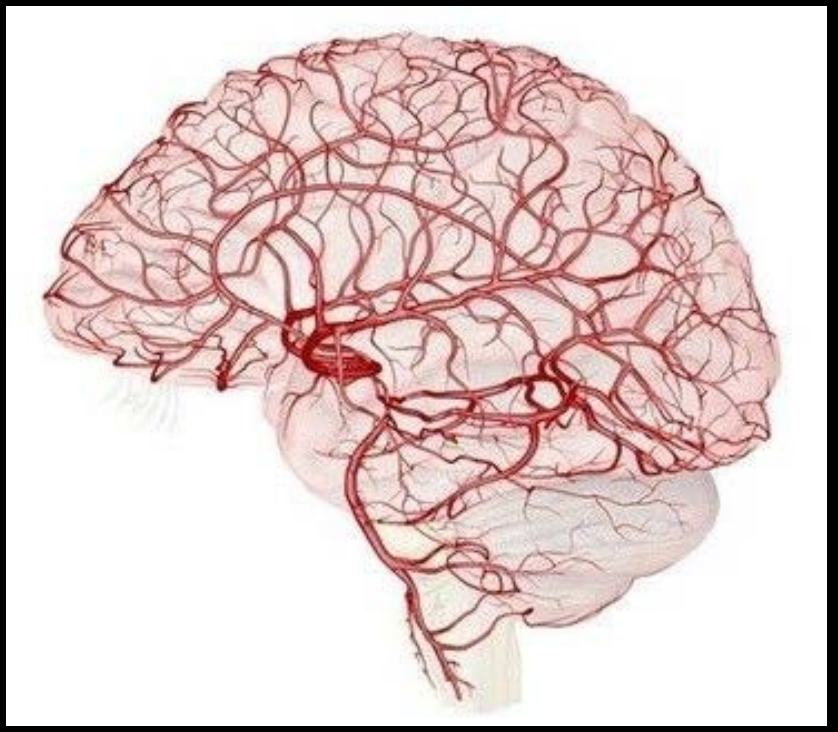
- **Hubs**
  - **Thrombectomy Stroke Centers**
    - --PSC level care, plus
    - --Endovascular thrombectomy
  - **Comprehensive Stroke Centers**
    - --Able to care for complex patients
    - --Advanced treatments (i.e. coils, stents, IA recanalization, etc)
    - --Trained specialists in key areas (Vascular neurology, Neurointerventional procedures, Neurocritical Care, Vascular Neurosurgery)

Key Treatment Capabilities of TJC Stroke-Designated Hospitals

	IV Therapies in ED (tPA, Kcentra, etc)	Stroke Unit Inpt Management	Endovascular Thrombectomy	Neurosurgery Coiling NeuroICU Care
Non-Stroke Hospital				
Acute Stroke Ready Hospitals (ASRH)	√			
Primary Stroke Centers (PSC)	√	√		
Thrombectomy Stroke Centers (TSC)	√	√	√	
Comprehensive Stroke Centers	√	√	√	√

Identifying Likely Large Vessel Occlusion Patients in Field

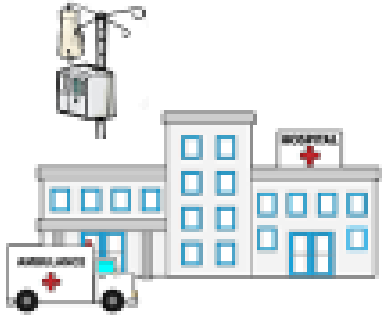
- Medium (distal) vessel and small (penetrator) occlusions
  - » IV tPA - works well, want asap
  - » Thrombectomy – not an option
  - » → Primary Stroke Center or Acute Stroke Ready Hospital
- Large vessel occlusions
  - » IV tPA - works poorly
  - » Thrombectomy – works well
  - » → Thrombectomy Stroke Center or Comprehensive Stroke Center



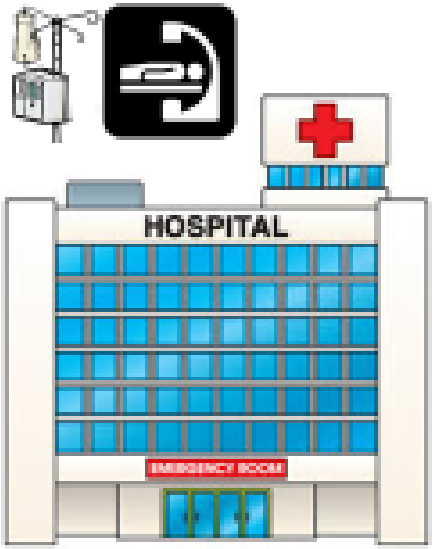
Organizing Regional Stroke Systems

One Tier EMS Stroke Routing

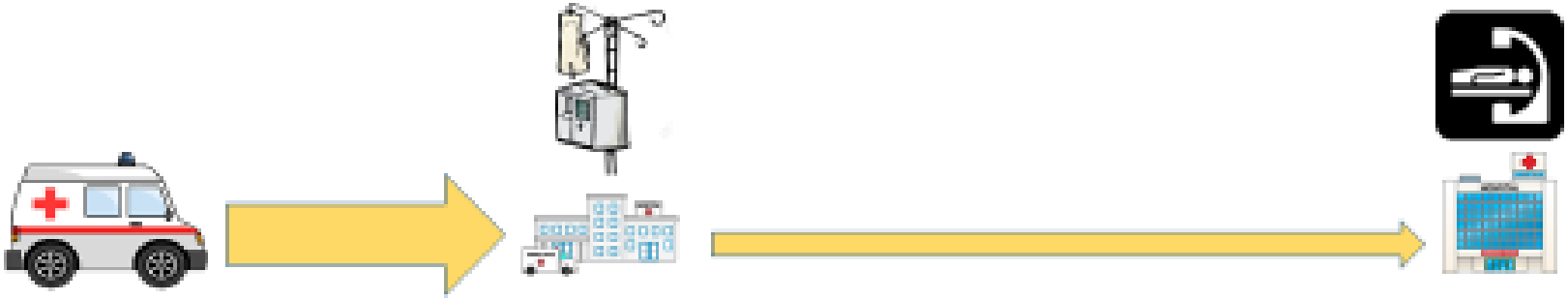
NonSC



PSC or ASR



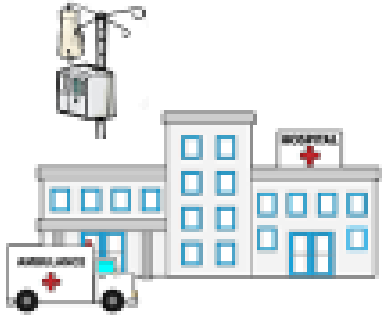
CSC



Organizing Regional Stroke Systems

One Advanced Tier EMS Stroke Routing

NonSC



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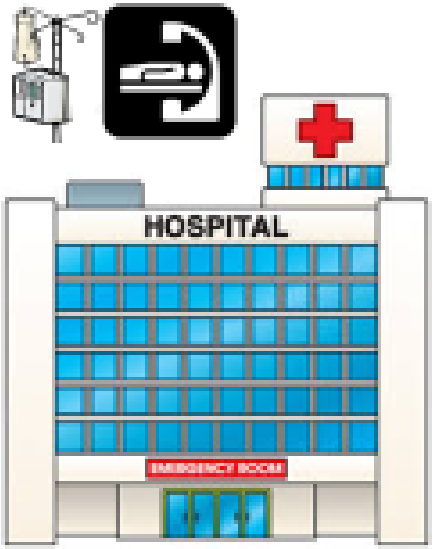
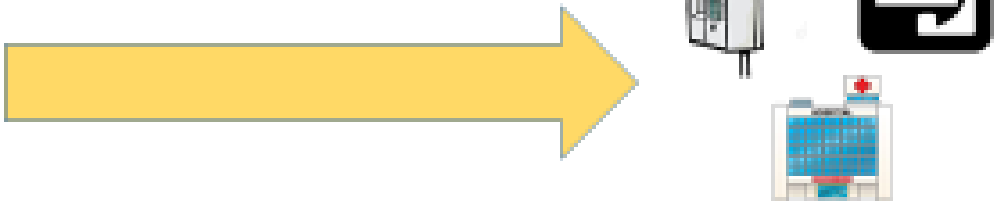
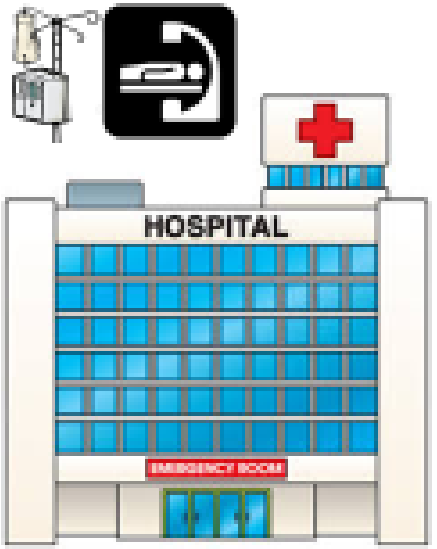


CSC

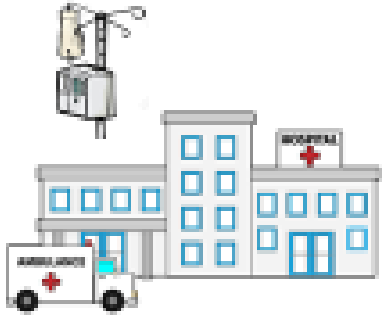


Organizing Regional Stroke Systems

Two Tier EMS Stroke Routing



NonSC



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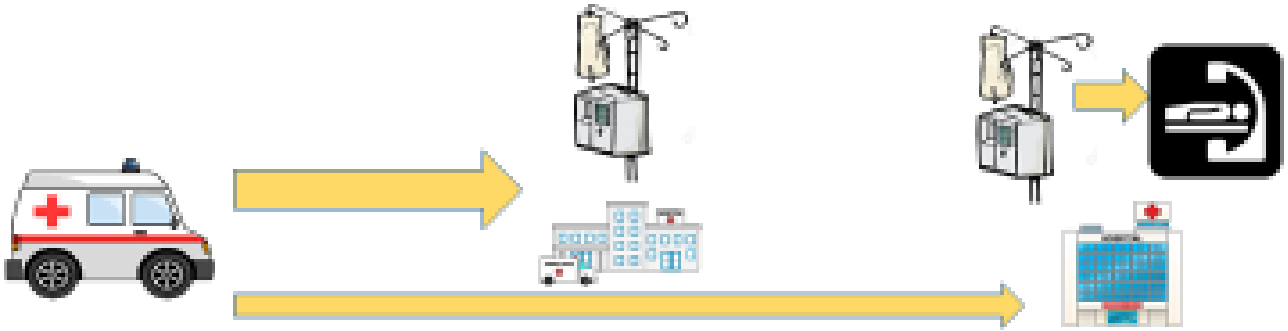

Examples of Prehospital Stroke Scales to Identify LVO / CSC-Approp

- Los Angeles Motor Scale (LAMS)
  - 3 elements
  - Facial droop, arm drift, grip weakness
- 3 Item Stroke Scale (3I-SS)
  - 6 elements
  - Level of consciousness, gaze deviation, facial droop, arm drift, R/L leg weakness
- Rapid Arterial OcClusion Evaluation Score (RACE)
  - 7 elements
  - Facial droop, arm drift, R/L leg weakness, gaze deviation, aphasia, denial of hemiparesis
- Cincinnati Prehospital Stroke Severity Scale (CPSSS)
  - 4 elements
  - Gaze deviation, arm drift, LOC command, LOC questions
- Field Assessment Stroke Triage for Emergency Destination (Fast-ED)
  - 5 elements
  - Face, Arm weakness, speech, eye deviation, Denial/Neglect
- VAN
  - 3 elements
  - Vision, Aphasia, Neglect

Variations in Scale Complexity
KISS Principle in Prehospital Care

LAMS	
Facial Droop	
Absent	0
Present	1
Arm Drift	
Absent	0
Drifts Down	1
Falls Rapidly	2
Grip Strength	
Normal	0
Weak Grip	1
No Grip	2

RACE	
Facial Palsy	
Absent	0
Mild	1
Mod-severe	2
Arm Motor Fxn	
Normal to mild	0
Moderate	1
Severe	2
Leg Motor Fxn	
Normal to mild	0
Moderate	1
Severe	2
Head + Gaze Dev	
Absent	0
Present	1
Aphasia (if right HP)	1
Normal to mild	0
Moderate	1
Severe	2
Agnosia (if left HP)	1
Normal to mild	0
Moderate	1
Severe	2

LAMS Comparable to or Better than 6 Other Proposed Prehospital LVO Scales and the Full NIHSS

LVO among All Acute Cerebral Ischemia Transports

	Sensitivity	Specificity	PPV	NPV	Accuracy
Prehospital					
LAMS	0.74	0.63	0.79	0.56	0.70
ED					
LAMS	0.63	0.79	0.85	0.53	0.69
CPSSS	0.54	0.88	0.89	0.50	0.66
FAST-ED	0.54	0.83	0.86	0.49	0.64
PASS	0.57	0.83	0.87	0.50	0.66
RACE	0.54	0.79	0.83	0.48	0.63
VAN	0.57	0.71	0.79	0.46	0.61
3i-SS	0.41	0.96	0.95	0.46	0.60
NIHSS ≥ 7	0.65	0.67	0.79	0.50	0.66
NIHSS ≥ 10	0.54	0.83	0.86	0.49	0.64

CSC-Appropriate (LVO+ICH) among All Suspected Stroke Transports

	Sensitivity	Specificity	PPV	NPV	Accuracy
Prehospital					
LAMS	0.70	0.68	0.84	0.49	0.69
ED					
LAMS	0.67	0.79	0.88	0.50	0.70
CPSSS	0.48	0.86	0.89	0.41	0.60
FAST-ED	0.53	0.82	0.88	0.43	0.62
PASS	0.55	0.82	0.88	0.43	0.63
RACE	0.56	0.79	0.86	0.43	0.63
VAN	0.59	0.71	0.83	0.43	0.63
3i-SS	0.38	0.93	0.93	0.39	0.54
NIHSS ≥7	0.71	0.68	0.84	0.50	0.70
NIHSS ≥ 10	0.56	0.82	0.88	0.44	0.64

--Noorian et al, Stroke 2018

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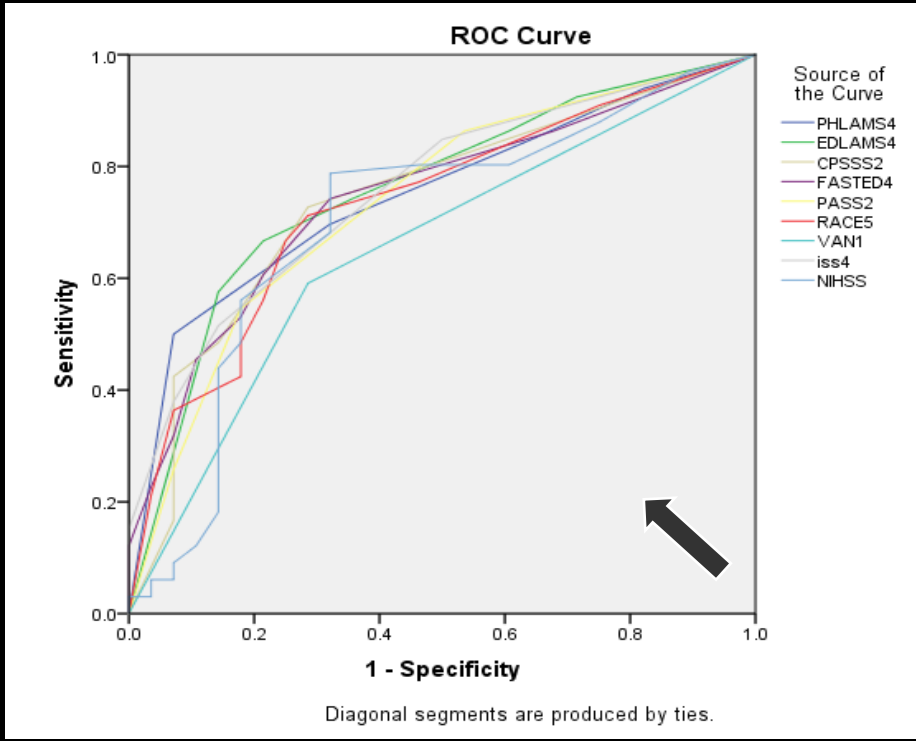
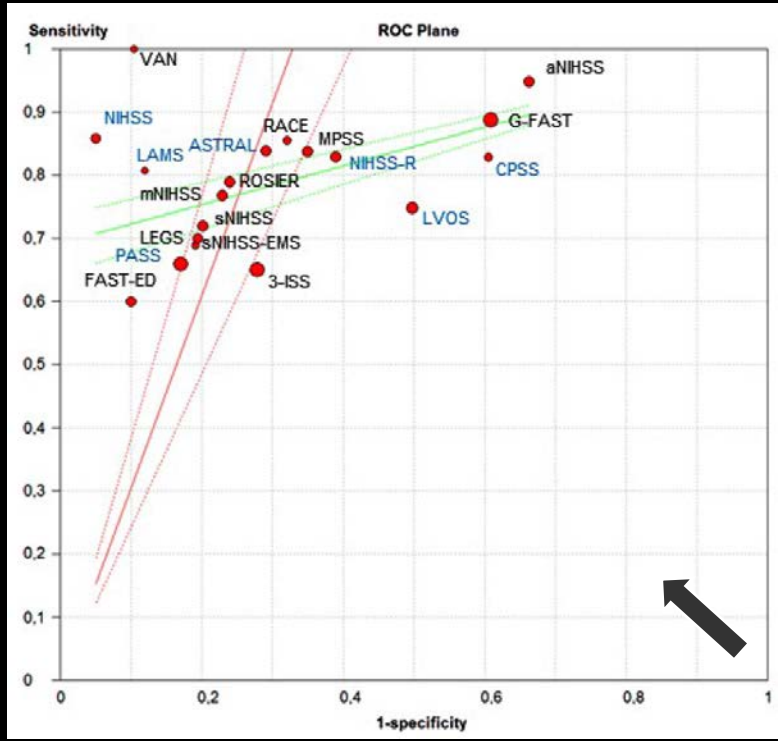
NIHSS ≥ 10	0.56	0.82	0.88	0.44	0.64

--Noorian et al, Stroke 2018

Comparative Scale Performance in Identifying LVO among All Acute Cerebral Ischemia Patients



--Noorian et al, Stroke 2018



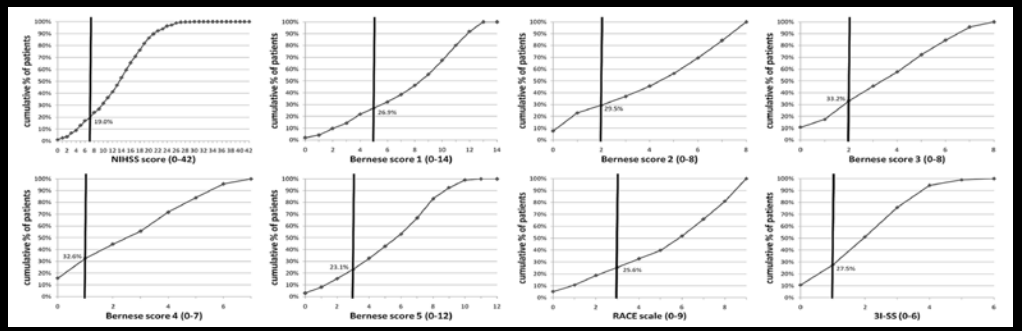
--Vidale et al, Acta Neurologica Scand 2018

Clinical prediction of large vessel occlusion in anterior circulation stroke: mission impossible?

--Heldner et al, J Neurol 2016

- 1085 consecutive patients
  - » Within 6h of LKW
  - » CTA or MRA
- Derived 5 data-driven NIHSS LVO pattern-specific scores
  - » Total NIHSS outperformed all pattern-specific scores
    - Best NIHSS cutoff ≥ 7
    - Sens 81%, Spec 77%

	Odds r
Best Gaze	9.60
Motor arms	7.60
Aphasia/neglect	7.13
Visual fields	7.00
Motor legs	5.78
LOC[a] altertness	5.64
Facial palsy	5.50
LOC[a] commands	4.50
LOC[a] questions	4.23
Dysarthria	3.20
Sensation	2.40
Limb ataxia	0.87



UCLA Stroke Center

Hyperacute Course Fluctuations - Constraint on All Prehospital Evaluations

1690 FAST-MAG Patients

Median LKW to Paramedic exam: 25 min

Median LKW to ED Study Nurse exam: 149 min

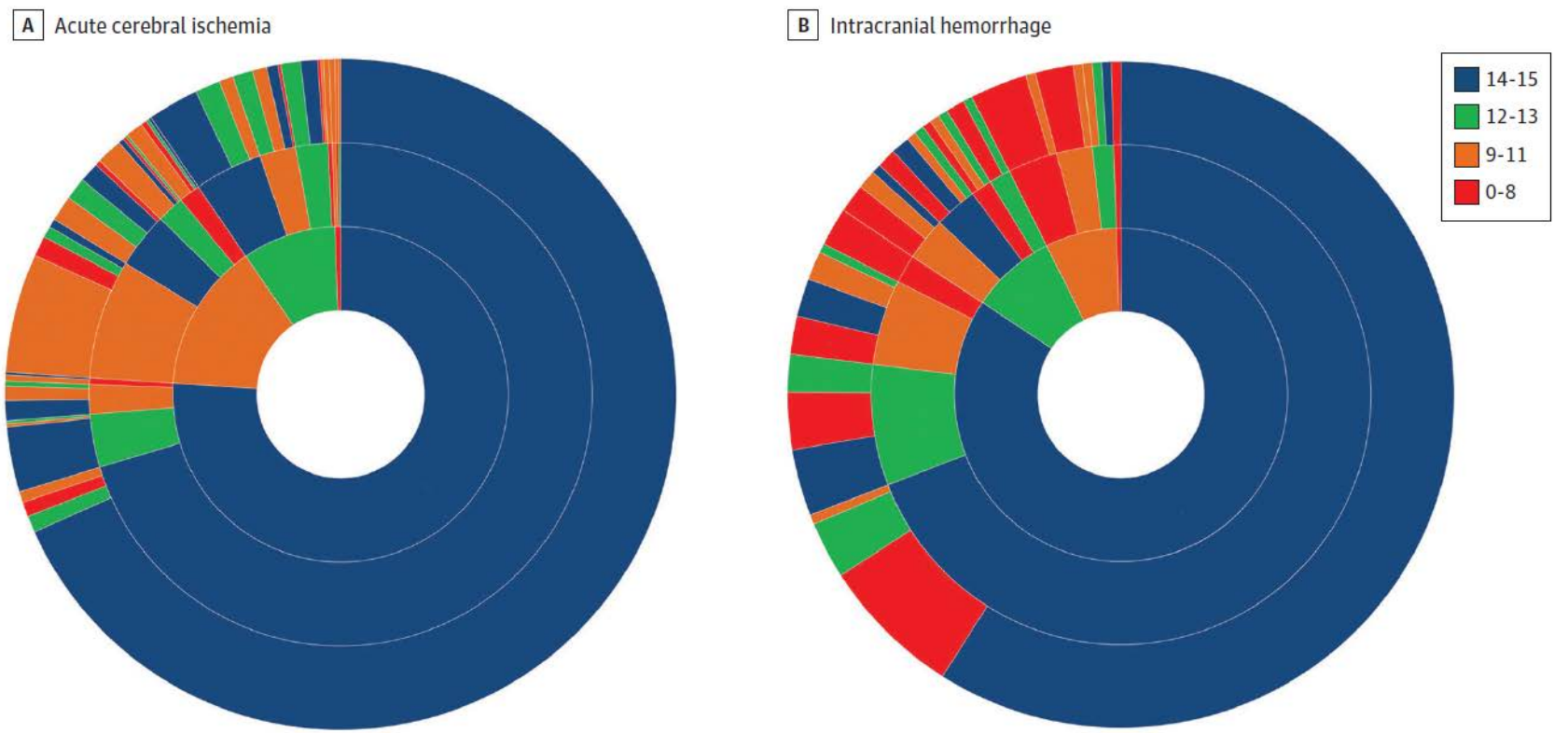
Stroke Type	Evolution from Ambulance to ED	Frequency
Acute Cerebral Ischemia	Substantial Improvement	31%
	Substantial Worsening	7%
	Stable	62%
Intracranial Hemorrhage	Substantial Improvement	5%
	Substantial Worsening	24%
	Stable	71%

--Tipirneni et al, ISC 2017; Shkirkova et al, JAMA Neurol 2018

Hyperacute Course Fluctuations - Constraint on All Prehospital Evaluations

1690 FAST-MAG Patients

Figure 1. Patterns of Glasgow Coma Scale (GCS) Score Evolution Among Patients With Acute Cerebral Ischemia or Intracranial Hemorrhage



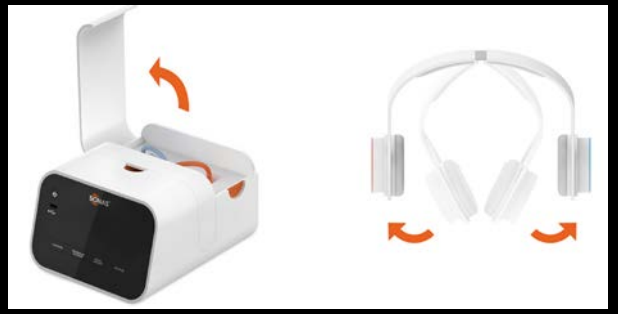
Stable 71%

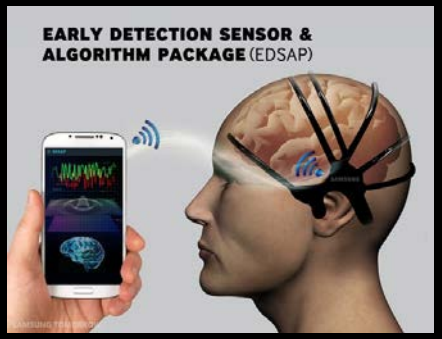
--Tipirneni et al, ISC 2017; Shkirkova et al, JAMA Neurol 2018

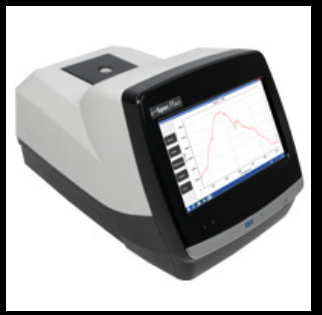
Figure 1 iTREAT ambulance setup with cradled iPad and suction mounting

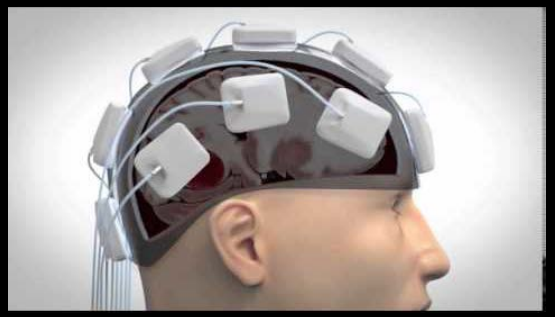
Mobile Stroke Diagnosis
Emerging Helmet Technologies

- Ultrasound
  - » Burl – Sonas
  - » Neural Analytics
- EEG
  - » Samsung – EDSAP
- Near infra-red
  - » B+W Tek – i-Spec
- Microwave
  - » Australia - Strokefinder helmet



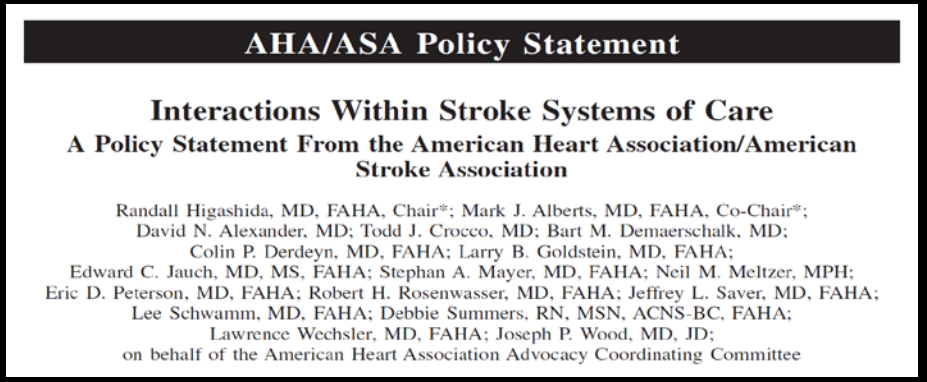






Routing Protocols in Tiered Systems: ASRHs, PSCs, CSCs (AHA-ASA 2013)

- Tiered routing options
  - » None
  - » Time (e.g. 3.5-6-24h)
  - » Severity (e.g. LAMS 4-5)
  - » Type (H/A, ICH)
- Considerations
  - » Urban v rural
  - » Geography
  - » Traffic
  - » Resources
  - » Minimize time out of service area



AHA/ASA Policy Statement

Interactions Within Stroke Systems of Care

A Policy Statement From the American Heart Association/American Stroke Association

Randall Higashida, MD, FAHA, Chair*; Mark J. Alberts, MD, FAHA, Co-Chair*; David N. Alexander, MD; Todd J. Crocco, MD; Bart M. Demaerschalk, MD; Colin P. Derdeyn, MD, FAHA; Larry B. Goldstein, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Stephan A. Mayer, MD, FAHA; Neil M. Meltzer, MPH; Eric D. Peterson, MD, FAHA; Robert H. Rosenwasser, MD, FAHA; Jeffrey L. Saver, MD, FAHA; Lee Schwamm, MD, FAHA; Debbie Summers, RN, MSN, ACNS-BC, FAHA; Lawrence Wechsler, MD, FAHA; Joseph P. Wood, MD, JD; on behalf of the American Heart Association Advocacy Coordinating Committee

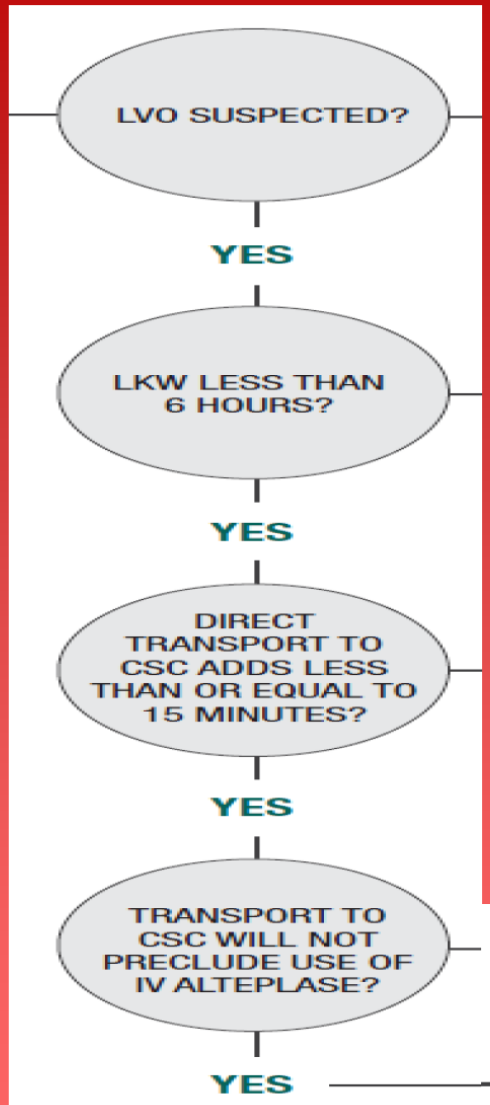
Severity-Based Stroke Triage Algorithm for EMS

* **What It Is:**

Evidenced-based best-practice, multi-specialty review of currently available data for EMS Stroke Triage

* **What It Is Not:**

Prescription or EXACT template to be followed word-for-word in every region



Go Directly to CSC IF:

Severity Screen (++)

+

LKW < 6 Hours

+

Transport to CSC Adds < 15 min

+

Transport to CSC Does Not Place Patient Outside Thrombolysis Window

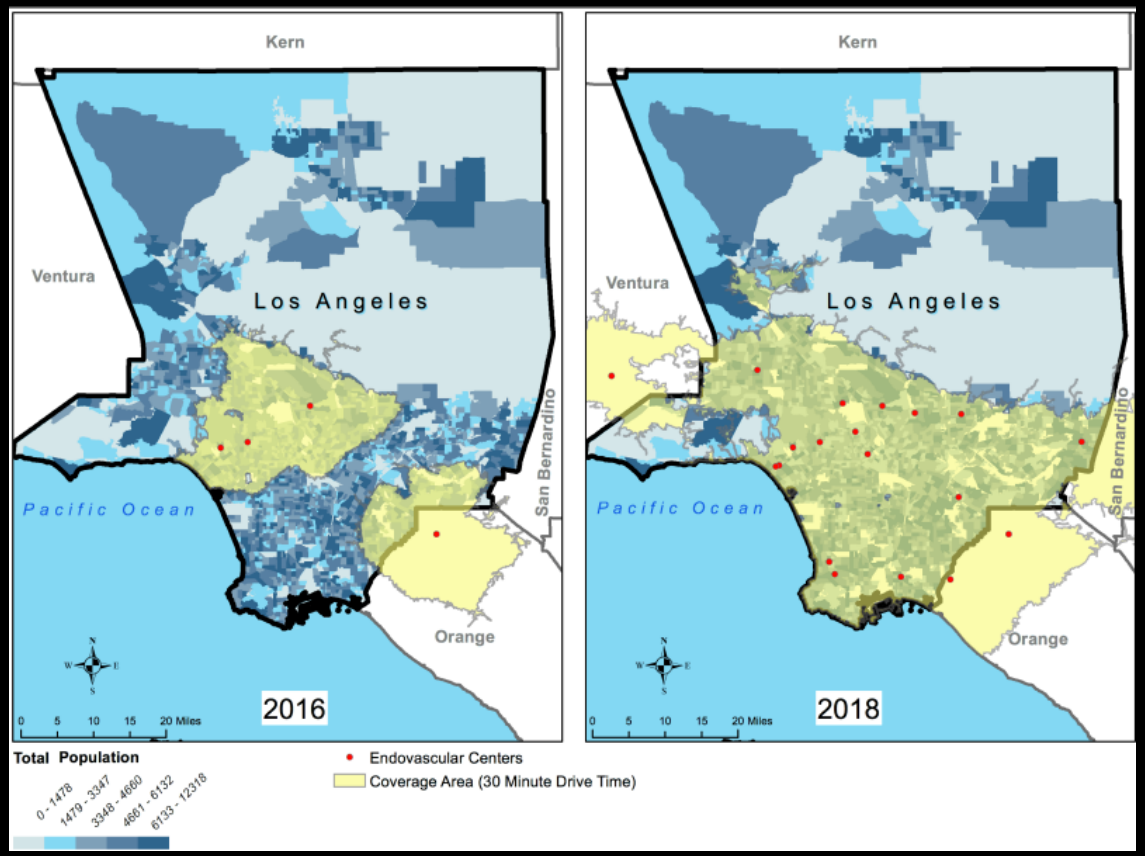
Any 'NO' then Go to Nearest/Closest Appropriate Facility Per Regional Plan

Call Stroke Alert, pre-notify receiving facility and transport directly to an appropriately certified CSC that is within the acceptable transport time, if no CSC meets the criteria then transport to the nearest designated EVT-capable center, or closest appropriate stroke center (ASRH,PSC) per your regional stroke system of care plan

Los Angeles County Two-Tier EMS Stroke Routing

- Population and Resources
  - » 10.1 million individuals
  - » 31 EMS agencies, 161 ambulances (1 MSU)
  - » 50 designated stroke hospitals (~30 PSC, 5 TSC, 15 CSC)
- New routing policy - 2018
  - » If suspected stroke (mLAPSS positive)
  - » Direct to nearest CSC or TSC, if
    - » ≥ 4, likely LVO if ACI, AND,
    - » Last known well is within 24h, AND
    - » TSC or CSC is within 30 mins
  - » Otherwise, direct to PSC
    - Accelerated inter-facility transfer if needed

Initial Impact of Two-Tiered Routing in a Major Metropolitan Region (LA)



Access to Endovascular Treatment within a 30 minute transport:

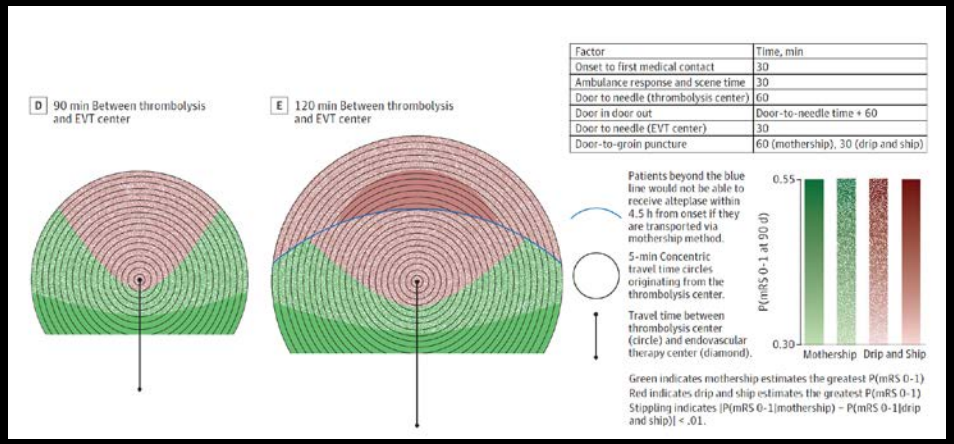
40% → 93%

ODDS RATIOS FOR OUTCOMES

	Pre	Post
TPA Administration	23.4%	26.6%
	OR 1.2, 95% CI 1.03-1.4	
Thrombectomy	5.2%	13.5%
	OR 2.8, 95% CI 2.3-3.8	
Inter-facility Transfer	3.5%	1.1%
	OR 0.3, 95% CI 0.2-0.5	

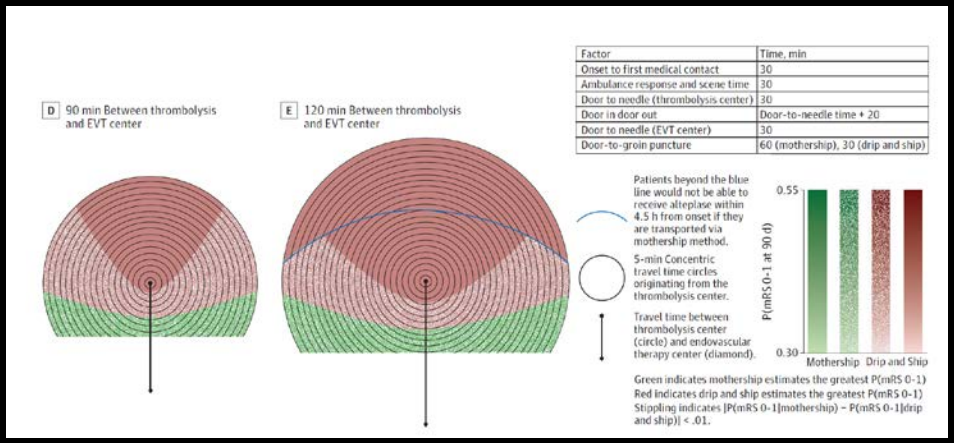
--Bosson et al, ISC 2019

Optimal workflows all sites



Factor	Time, min
Onset to first medical contact	30
Ambulance response and scene time	30
Door to needle (thrombolysis center)	60
Door in door out	Door-to-needle time + 60
Door to needle (EVT center)	30
Door-to-groin puncture	60 (mothership), 30 (drip and ship)

Slower workflow at PSCs



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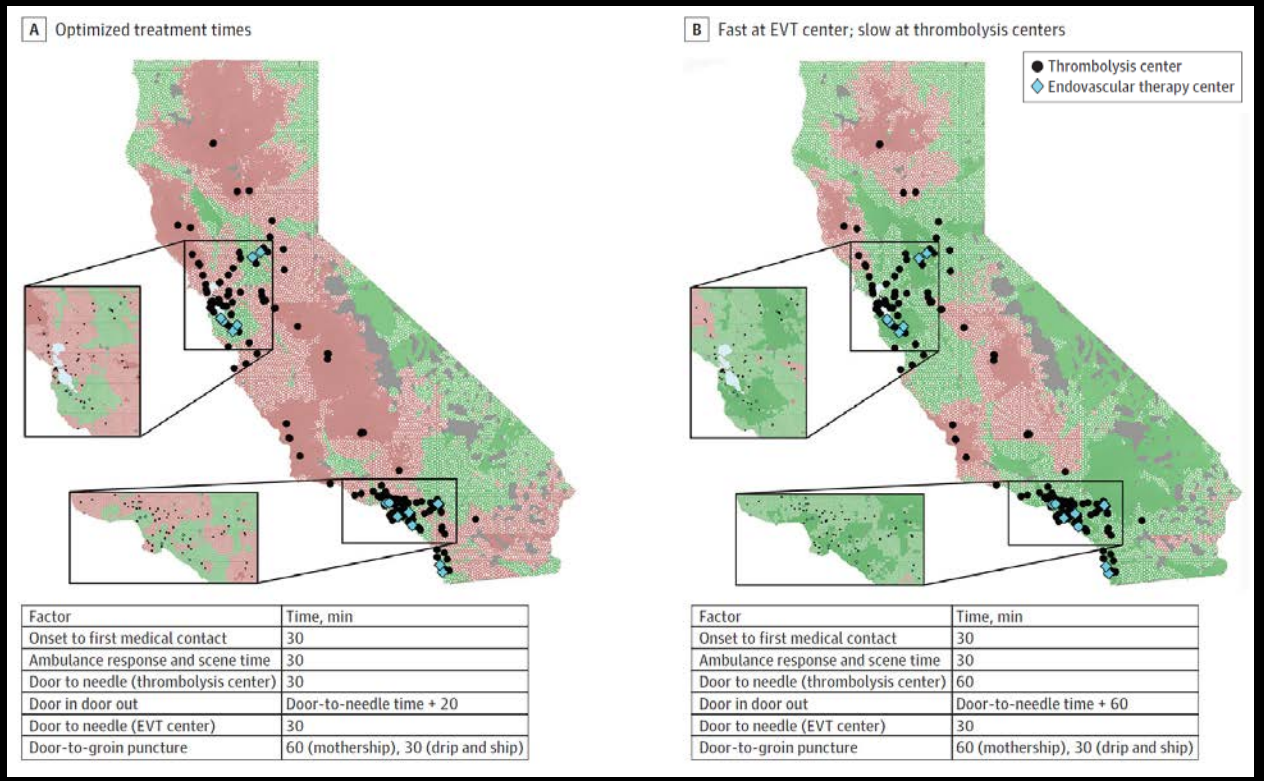

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--Holodinsky et al, JAMA Neurol 2018

Geographic Influences on Stroke Systems of Care

Geographic Influences on Stroke Systems of Care

- Horizontal over land
  - » Most regions
    - Ground/air ambulance

Geographic Influences on Stroke Systems of Care

- Horizontal over land
  - » Most regions
    - Ground/air ambulance
- Vertical over land
  - » Norway/Colorado/Bavaria
    - Helicopter

Geographic Influences on Stroke Systems of Care

- Horizontal over land
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- Vertical over land
  - » Norway/Colorado/Bavaria
    - Helicopter
- Subterranean under traffic
  - » Manhattan
    - Subway





Geographic Influences on Stroke Systems of Care

- Horizontal over land
  - » Most regions
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- Vertical over land
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    - Helicopter
- Subterranean under traffic
  - » Manhattan
    - Subway
- Horizontal over water
  - » Hawaii
    - Boat/air ambulance

Geographic Influences on Stroke Systems of Care

- Horizontal over land
  - » Most regions
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- Vertical over land
  - » Norway/Colorado/Bavaria
    - Helicopter
- Subterranean under traffic
  - » Manhattan
    - Subway
- Horizontal over water
  - » Hawaii
    - Boat/air ambulance
- Horizontal over snow
  - » Alaska
    - Dogsled

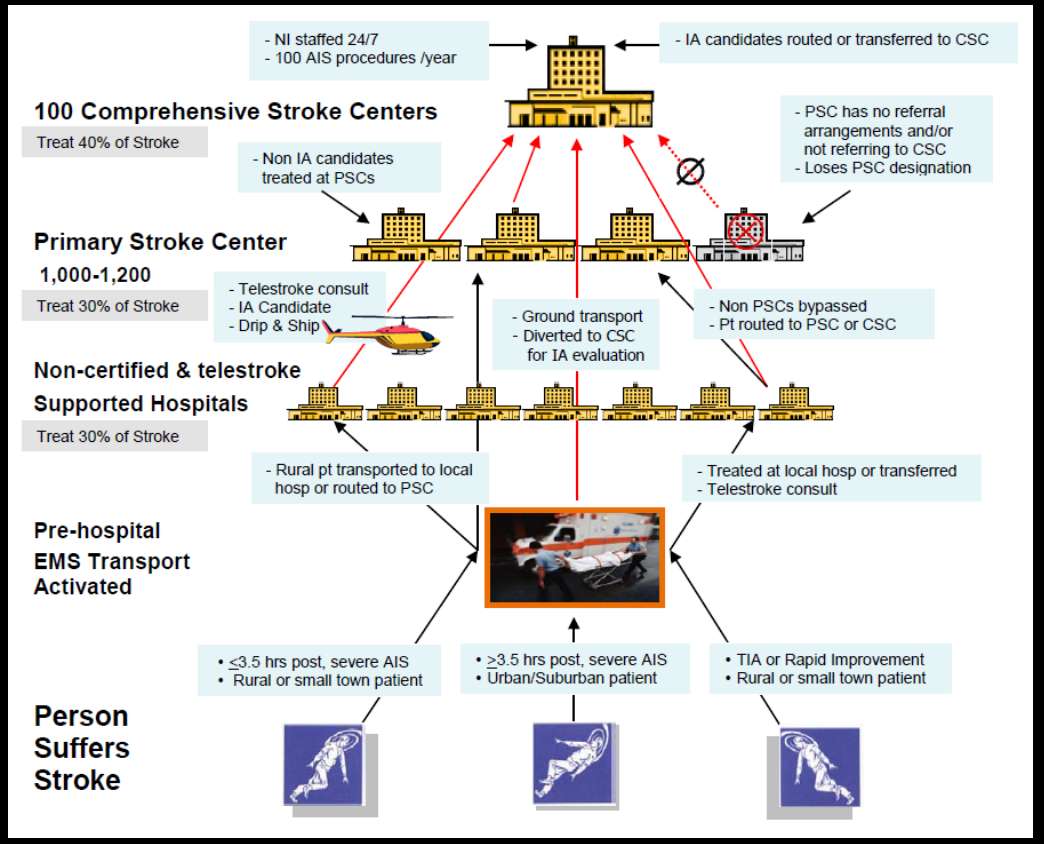






Systems of Care Trials

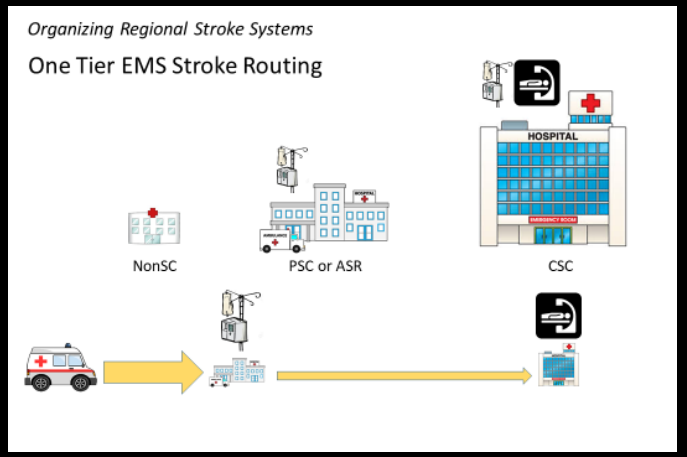
- Systems of care
  - » Drip and ship
    - Faster IV TPA, slower cath
  - » Mothership
    - Slower IV TPA, faster cath
  - » BATmobile trip (mobile CT)
    - Fastest IV TPA, fast cath
- Trial designs
  - » Cluster Control
  - » Stepped wedge

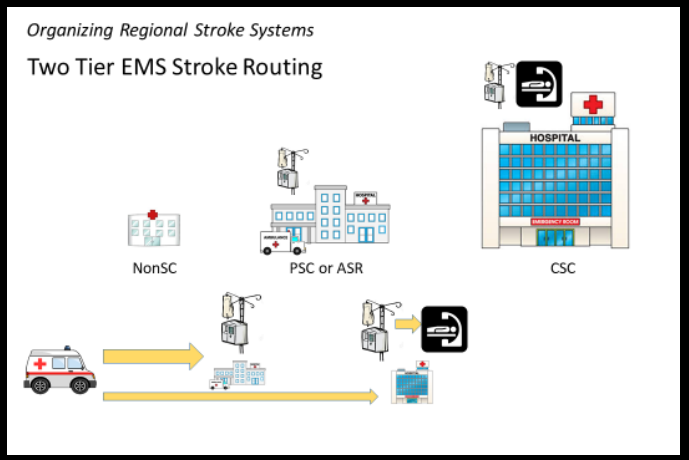


--Saver et al, The Stroke Interventionalist 2013

RACECAT Trial

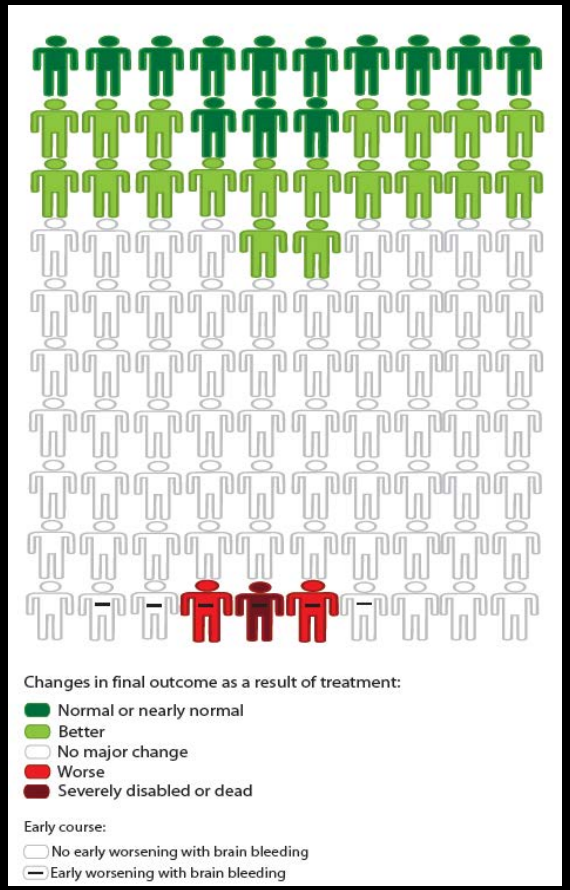
- Cluster-control RCT Spain
  - » 12 hospitals, 1754 patients
- Key entry criteria
  - » LVO by RACE and teleneurology
  - » Can reach an EVT-SC within 7h of onset
- Randomized strata
  - » Daytime vs evening
  - » Weekday vs weekend
  - » Urban vs rural
- Outcome: mRS 0-2
- Timeline: 2017-2020



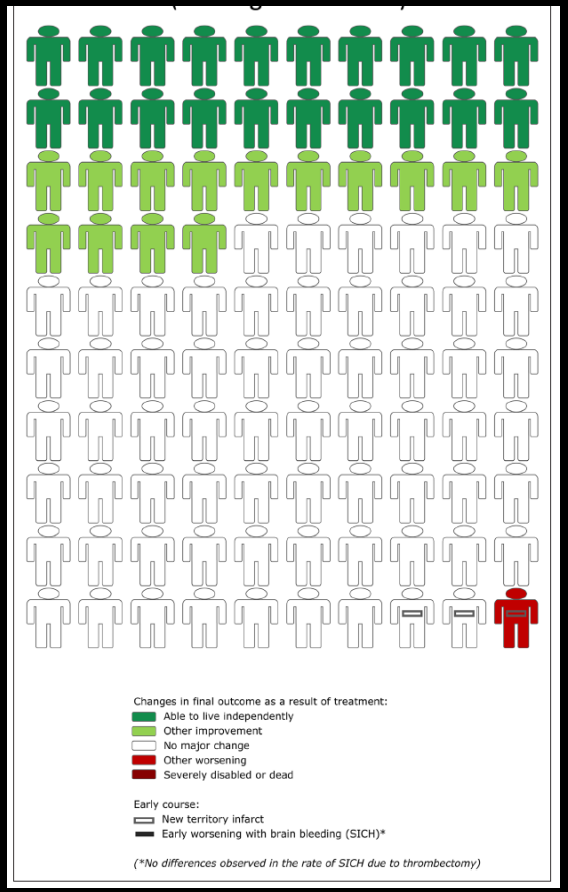


Patient/Family Decision Aids

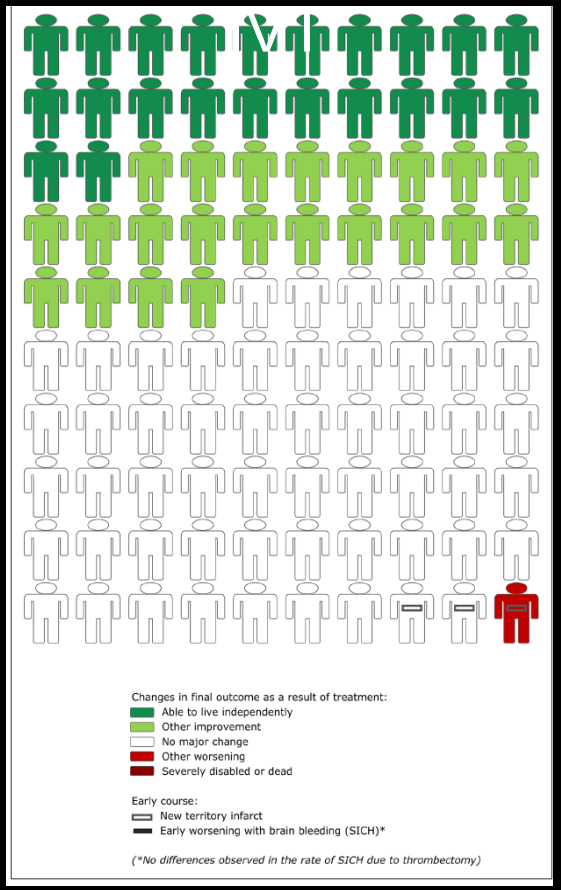
IV TPA vs Control



EVT+IVT vs IVT



EVT vs Control

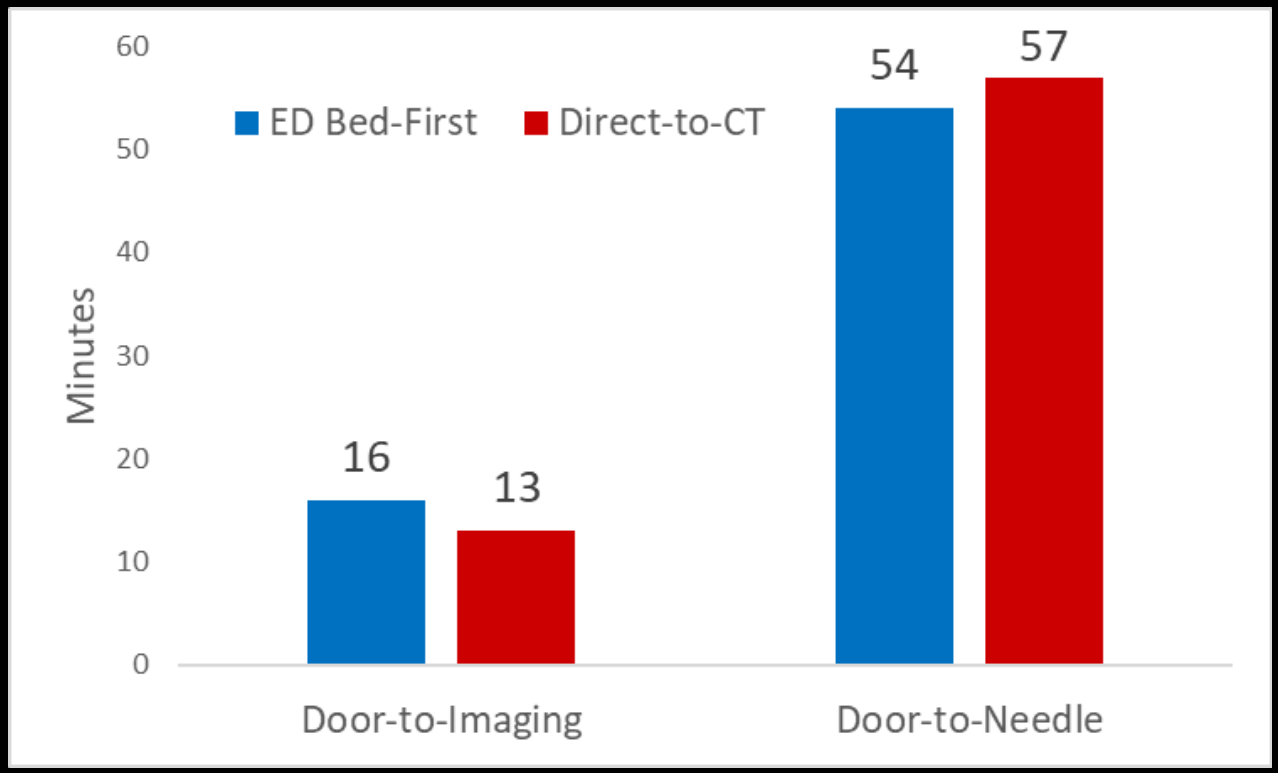


--Gadhia et al, Stroke 2010

--Tokunboh et al, Stroke 2010

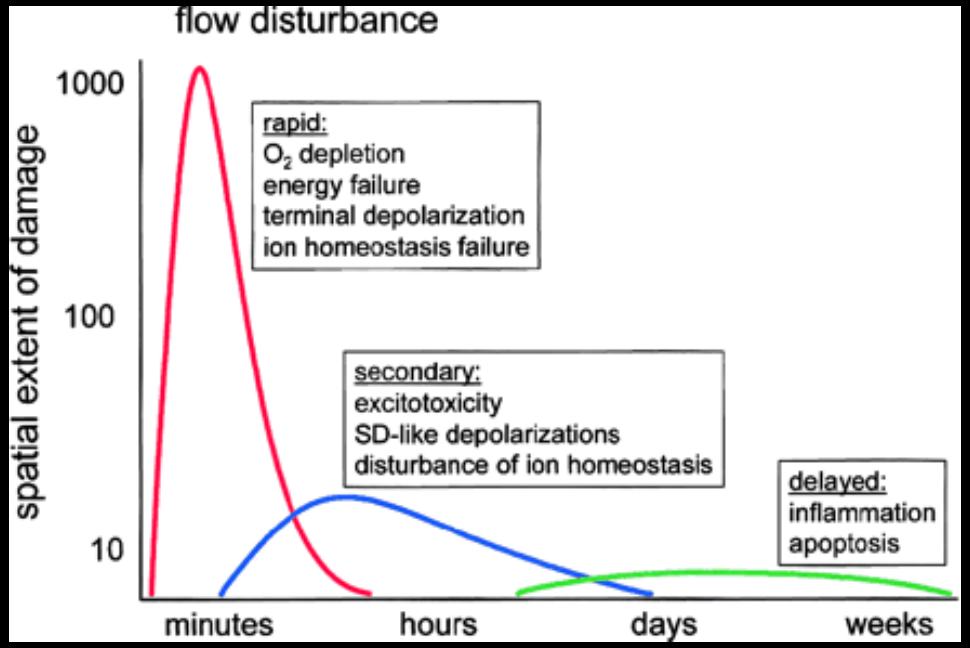
Does “Direct-to-CT” Routing Shorten Door-to-Needle Times?

- LA EMS stroke transports 5/15-4/16
  - » 46 receiving ASCs
- TPA treatment
  - » 789/6315 (13%)
  - » ED-Bed-First 681 (78%)
  - » Direct-to-CT 171 (22%)



--Sloane et a, JSCVD 2019, In Press

The Ischemic Cascade and Neuroprotective Interventions

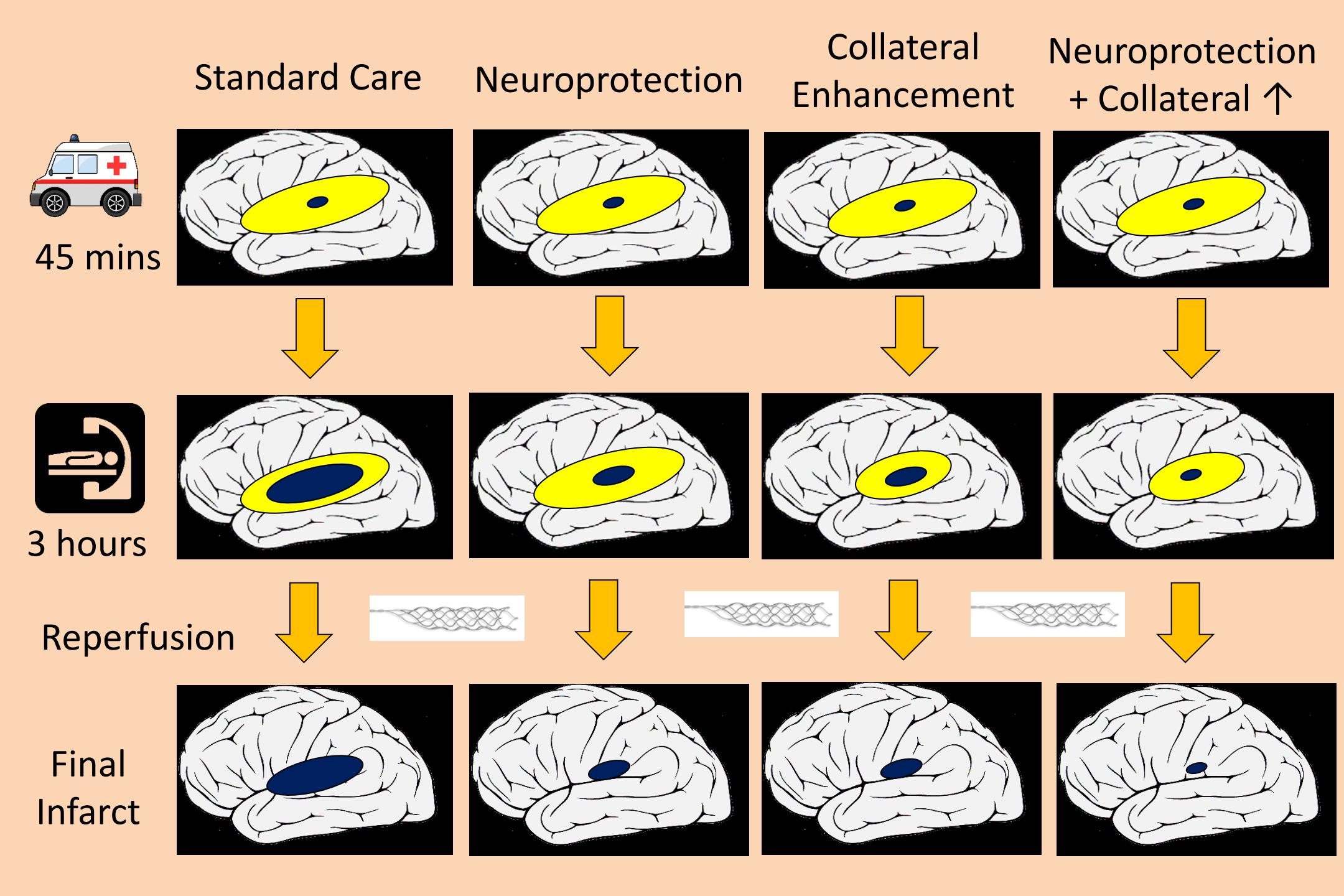


--Heiss et al, Stroke 1999

--Sanossian + Saver, In Press

UCLA Stroke Center

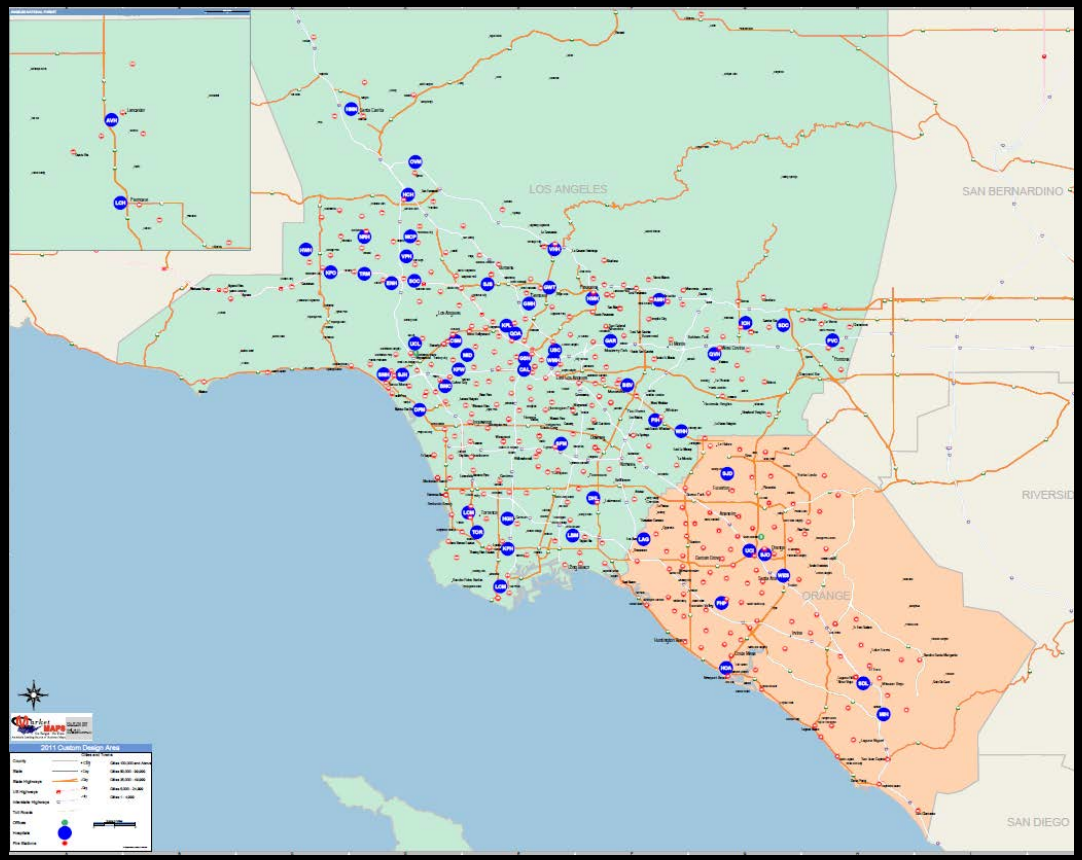
Category	Agents
Metabolism Suppressors	Hypothermia – profound* **Hypothermia – mild-moderate*** **Transcranial direct current stimulation**
Promoters of Genetically Programmed Hypoxia/Injury Tolerance and Repair	**Ischaemic per-conditioning*** Ischaemic post-conditioning* Growth factors*
Free Radical Scavengers and Antioxidants	**Uric acid*** **Edaravone*** Tirilazad* Disufenton sodium (NXY-059)* Ebselen
Promoters of Membrane Repair	**Citicoline***
Modulators of Excitatory Amino Acids	NMDA receptor antagonists* Dextrorphan* Ketamine Xenon Postsynaptic scaffolding proteins* NA-1* AMPA and other receptor antagonists
Modulators of Calcium Influx	Nimodipine* Flunarazine*
Sodium Channel Blockers	Fosphenytoin* Lidocaine
Modulators of GABA Inhibition	Clomethiazole* Diazepam*
Nitric Oxide Donors	**Glyceryl trinitrate*** L-arginine
Modulators of Carnitine + Mitochondrial Function	Mildronate Coenzyme Q10
Anti-Inflammatory	Enlimomab* Neutrophil inhibitory factor*
Oxygen Delivery Enhancers	Normobaric hyperoxemia Hyperbaric hyperoxemia* Aqueous oxygen **Trans sodium crocetate*** **Hemoglobin based oxygen carriers***
Multiple Leading Mechanisms	Statins* Minocycline* Magnesium* Albumin* Gangliosides* Melatonin
Uncertain Mechanism	Piracetam*


Standard Care
Neuroprotection
Collateral Enhancement
Neuroprotection + Collateral ↑
45 mins
3 hours
Reperfusion
Final Infarct

Prehospital Stroke Trials of Paramedic Delivered Therapy

Trial	Intervention	Strategy	Design	Size	Status
FAST-MAG Pilot	Magnesium	NP	Pilot / Hist Cont	20	2004
Helsinki EMS	IV + SQ Insulin	Homeostasis	Randomized (open-lab)	23	2011
Aarhus Univ	Remote perconditioning	NP	Randomized (open-lab)	443	2013
RIGHT	Glyceryl trinitrate	BP/NP	Randomized (open-lab)	41	2013
PIL-FAST	Lisinopril	BP	Randomized (open-lab)	14	2013
FAST-MAG Pivotal	Magnesium	NP	Randomized (placebo)	1700	2014
RIGHT-2	Glyceryl trinitrate	NP/BP/CE	Randomized (placebo)	850	2018
FRONTIER	NA-1	NP	Randomized (placebo)	500	Enrolling (Canada)
RESIST	Remote perconditioning	NP	Randomized (open-lab)	1500	Enrolling (Denmark)
PHAST-TSC	Trans Sodium Crocetinate	NP	Randomized (placebo)	160	Enrolling (LA + VA)

FAST-MAG Trial Consortium



Performance Sites in Los Angeles and Orange Counties, 2004-2012

- Los Angeles and Orange Counties
- Population 13.3 million
- 40 EMS Provider Agencies
  - » 315 rescue ambulances
  - » 2988 paramedics
- 60 receiving hospitals
  - » 952 physician-investigators
    - 715 Emergency Medicine (site PIs)
    - 210 Neurologist
    - 26 Nsurg/Intensiv/Hosp
- 95 CCC coordinators and research assistants

Supported by NIH-NINDS

FAST-MAG

FAST-MAG Time Intervals

	Placebo (n=843)	Magnesium (n=857)	Total (n=1700)	p value
Onset* to Drug (mins)	46 (36-62)	45 (35-60)	45 (35-62)	0.24
Onset* to Drug (category)				
0-1 hours	73.2%	75.3%	74.3%	0.61
1-2 hours	25.7%	23.7%	24.7%	
>2 hours	1.1%	0.9%	1.0%	
On Scene to Drug	23 (19-28)	23 (18-27)	23 (18-27)	0.58
On Scene to Door**	33 (27-39)	32 (27-39)	33 (27-39)	0.91

*Onset = last known well time

**Historical comparator, pretrial LA scene to door times = 35 minutes (Stroke 2004;35:e106-108)

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FAST-MAG

Reperfusion Treatments After Arrival in FAST-MAG Cerebral Ischemia Patients (n=1235)

	Number of Patients	Percent
IV tPA	452	36.6%
Endovascular	76	6.1%

Needle to Needle Time
(prehospital study drug to ED tPA):
median 95 minutes

--Nguyen P, Sanossian N, et al, ISC

Supported by NIH-NINDS

FAST-MAG

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IV tPA	**452**	**36.6%**
Endovascular	**76**	**6.1%**

Needle to Needle Time
(prehospital study drug to ED tPA):
median 95 minutes
Est Needle to Endo Reperf Time: 140 min

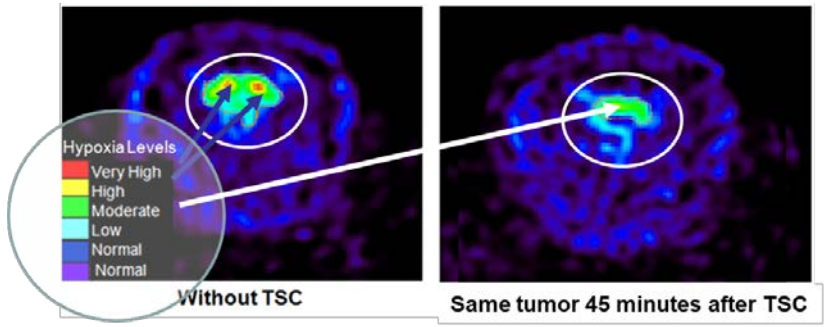
--Nguyen P, Sanossian N, et al, ISC

Supported by NIH-NINDS

FAST-MAG

Pre-Hospital Administration of Stroke Therapy (PHAST-TSC) Trial

- Testing Trans Sodium Crocetinate (TSC)
  - Oxygen diffuser enhancer
  - Reduces stroke size in animal models
  - Reduces tissue hypoxia in phase 2 human trials in PAD and glioma
- PHAST-TSC design
  - Phase 2 safety and preliminary efficacy trials
  - 160 prehospital patients under 2h from onset
  - ~150 ambulances and 30 receiving Stroke Centers, Los Angeles and Virginia
  - Funded by Diffusion Pharmaceuticals, Inc. of Charlottesville, VA



PET scan showing hypoxia levels in rat brain tumor, before and after TSC.

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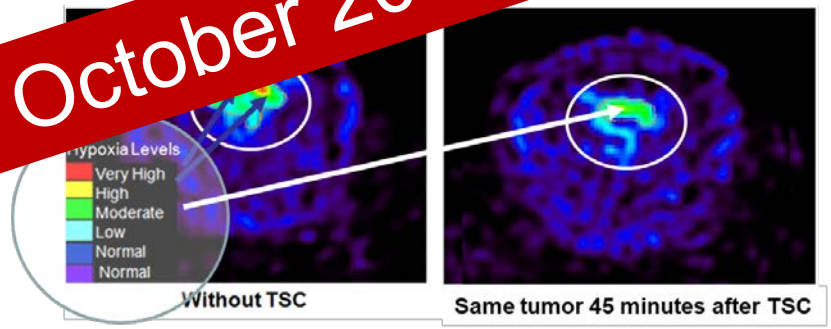
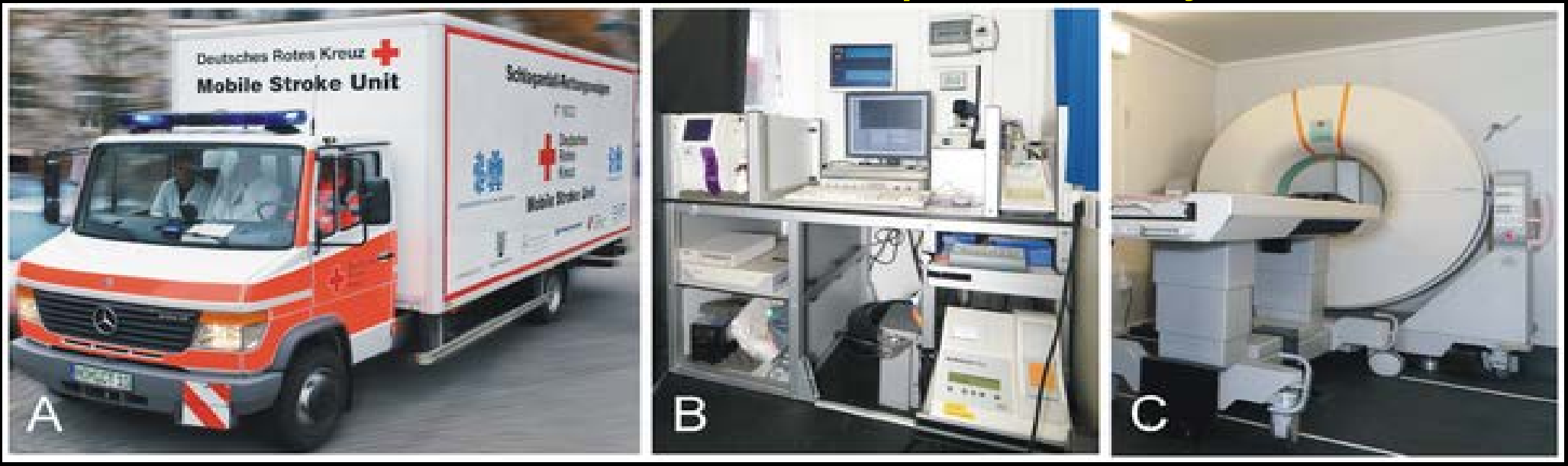
First Patient Enrolled – October 2019

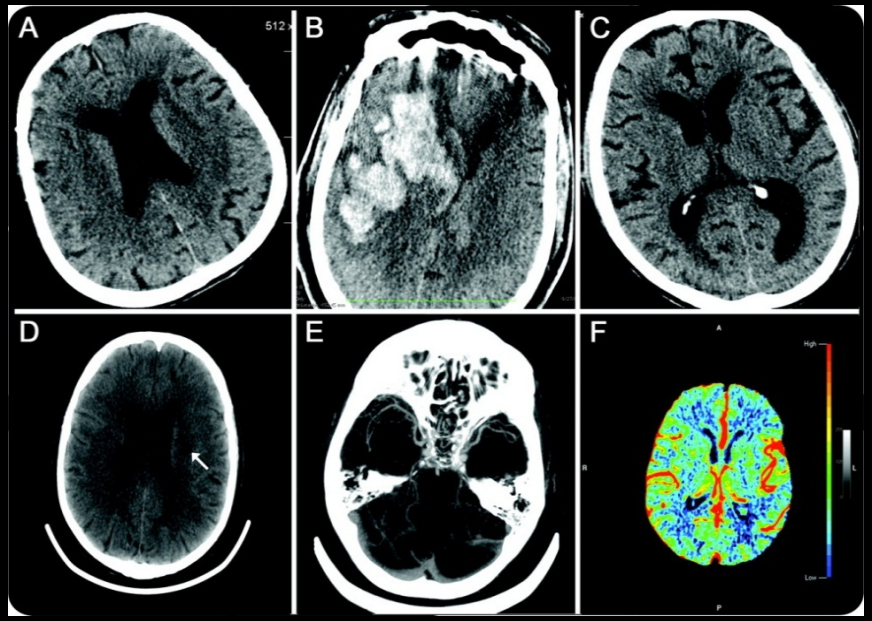


PET scan showing hypoxia levels in rat brain tumor, before and after TSC.

Control (normal saline)-treated TSC-treated

Mobile Stroke Units for Prehospital Thrombolysis



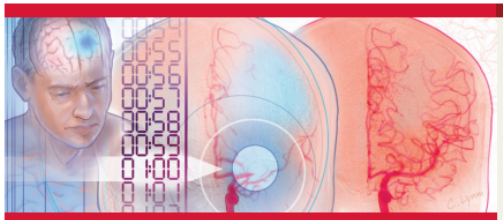


--Walter et al, PLOS One, 2010, Homburg

--Audebert et al, Berlin

In This Issue of JAMA

April 23/30, 2014
Volume 311, Number 16
Pages 1579-1704



Neurology

Edited by Roger N. Rosenberg, MD, and Jeffrey L. Saver, MD

Editor in Chief
Howard Bauchner, MD

130 YEARS
OF CONTINUOUS
PUBLICATION

Research

Original Investigation

Effect of the Use of Ambulance-Based Thrombolysis on Time to Thrombolysis in Acute Ischemic Stroke
A Randomized Clinical Trial

Martin Ebinger, MD; Benjamin Winter, MD; Matthias Wendt, MD; Joachim E. Weber, MD; Carolin Waldschmidt, MD; Michal Rozanski, MD; Alexander Kunz, MD; Peter Koch, MD; Philipp A. Kellner, MD; Daniel Gierhake, MD; Kersten Villringer, MD; Jochen B. Fiebach, MD; Ulrike Grittner, PhD; Andreas Hartmann, MD; Bruno-Marcel Mackert, MD; Matthias Endres, MD; Heinrich J. Audebert, MD; for the STEMO Consortium

--JAMA, April 2014

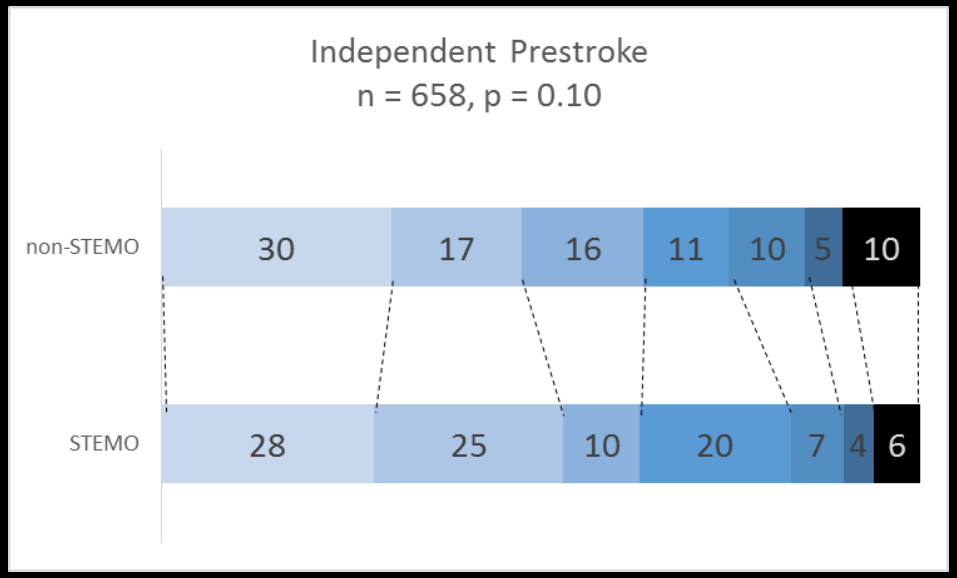
UCLA Stroke Center

PHANTOM-S Trial
TPA Frequency and Speed

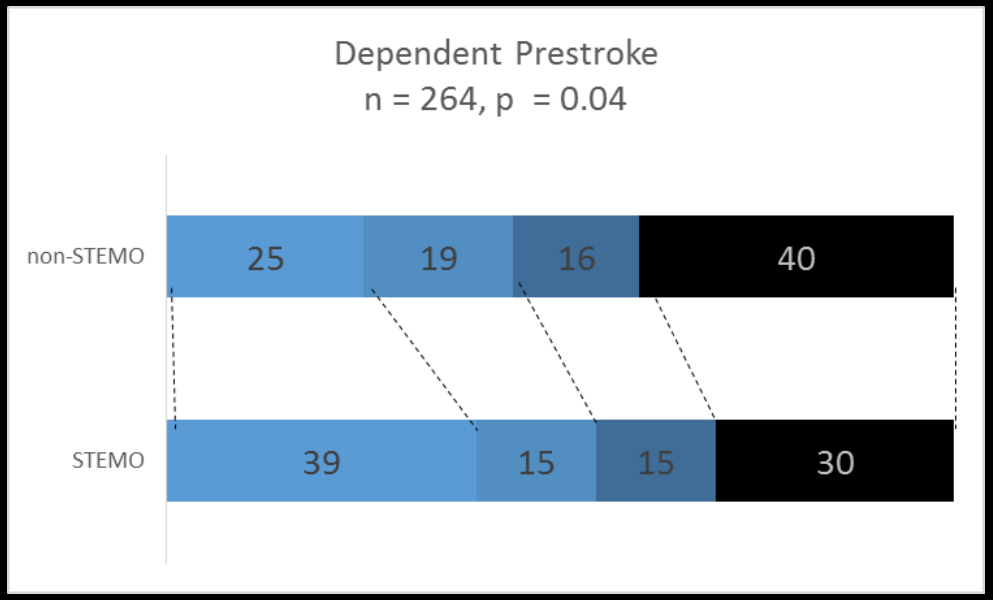
	CT Ambulance Patients	p value	CT Ambulance Weeks	p value	Control Weeks
N	1804		3213		2969
Pct of AIS	32.6%	<0.001	28.9%	<0.001	21.1%
DTN Hosp (min)					42
Alarm to Hosp (min)	85	<0.001	67	<0.001	35
Alarm to Imaging	38	<0.001	44	<0.001	52
Imaging to TPA	14	<0.001	17	<0.001	24
*Alarm to TPA	52	<0.001	61	<0.001	76
Onset to TPA	103	<0.001	110	0.003	119
Onset to TPA <90m	58%	<0.001	48%	0.02	37%

*Primary Endpoint

Disability Outcomes in STEMO Studies Suggestive of Benefit



--Kunz et al, Lancet Neurol 2016

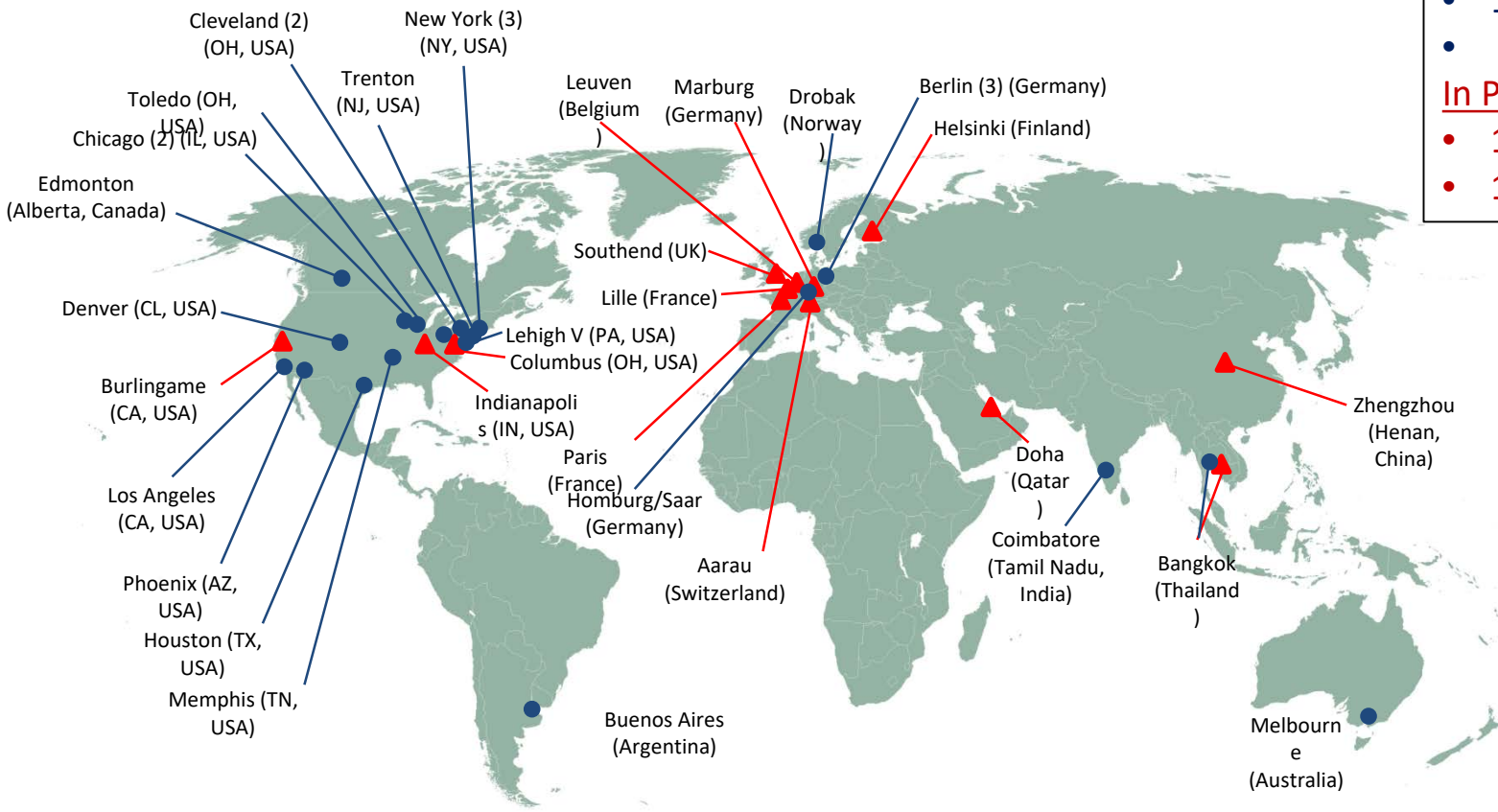


--Nolte et al, Stroke 2018

World Map of Mobile Stroke Unit Projects

Active
- 22 Units
- 16 cities
- 5 continents

In Process
- 13 Units
- 12 cities



sites with active mobile stroke units

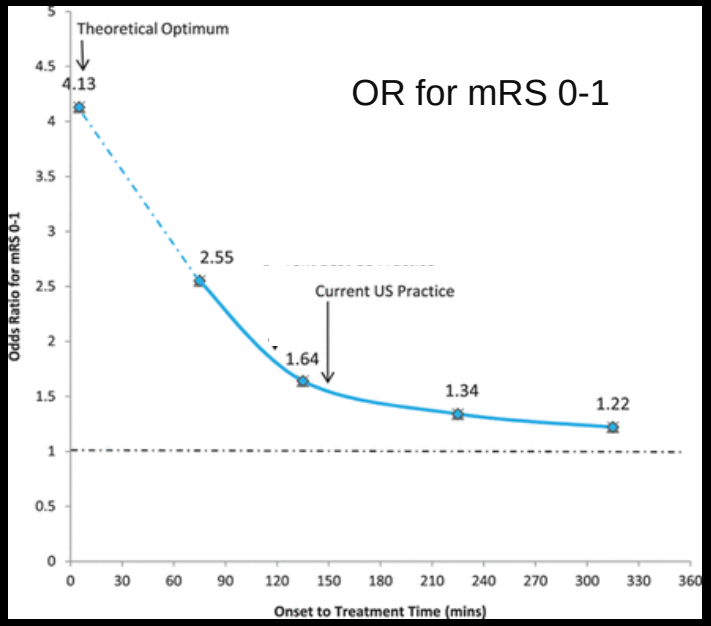
sites with projects in planning or implementation state

Modifed from Lesmeister/Fassbender 2018

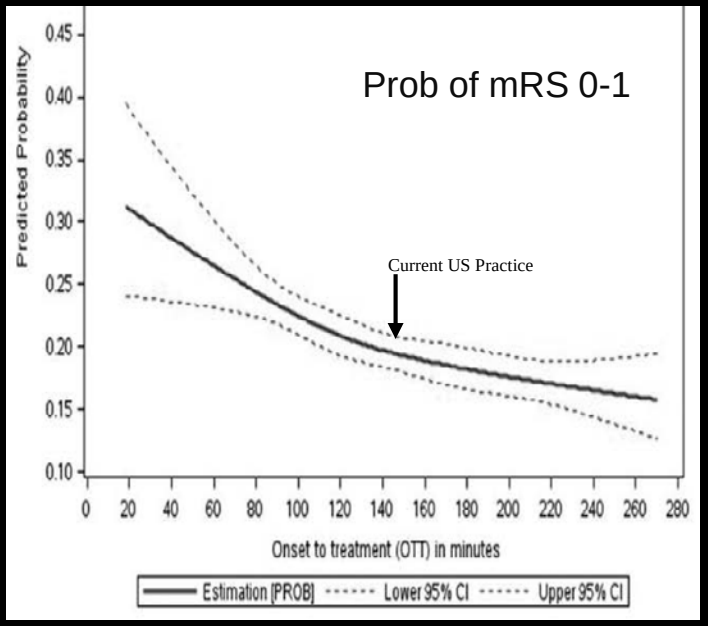
UCLA Stroke Center

Onset to Treatment Time for IV TPA and Excellent Outcome

RCTs (8 trials)
3760 patients



GWTG-Stroke
65,384 patients



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--Lees et al, Lancet 2010; Saver + Levine, Lancet 2010; Saver, Stroke 2012; Audebert et al, JAMA 2014; Kim JT et al. Circulation 2017

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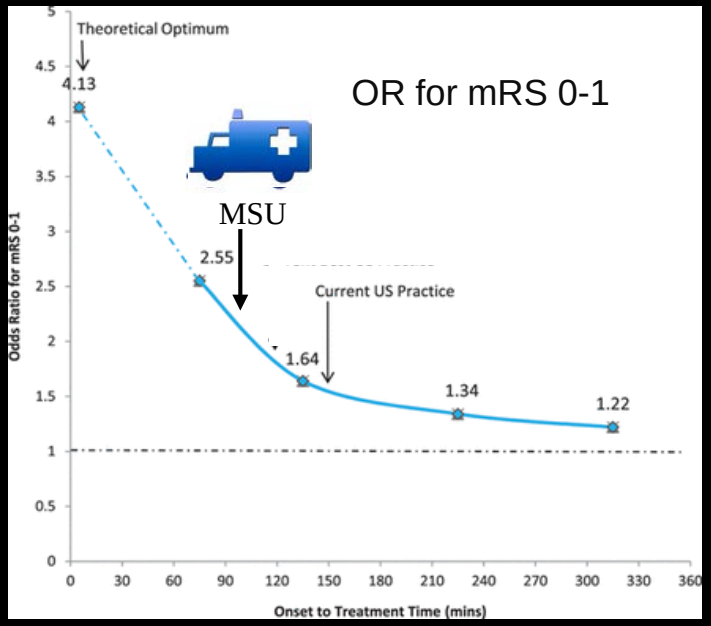

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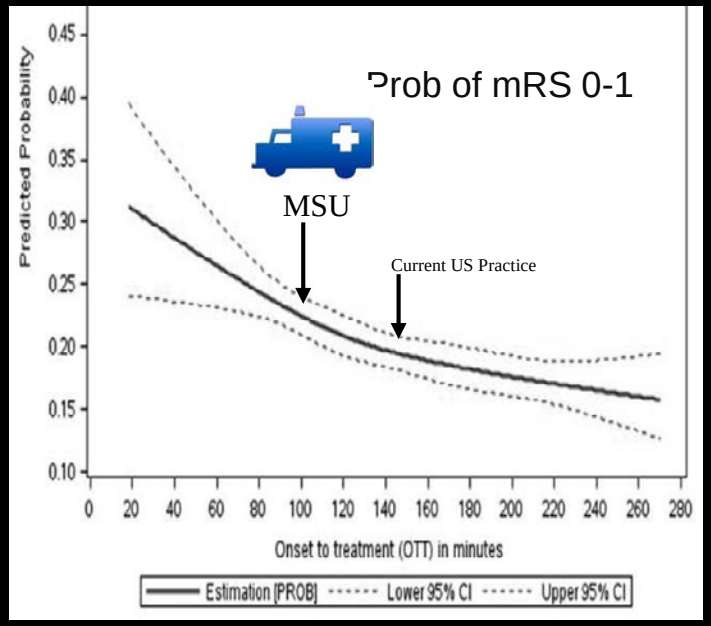

UCLA Stroke Center

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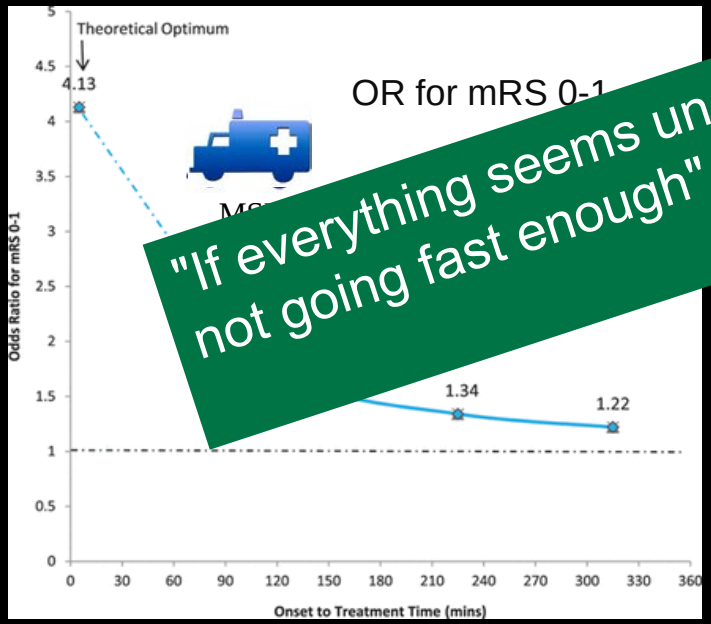
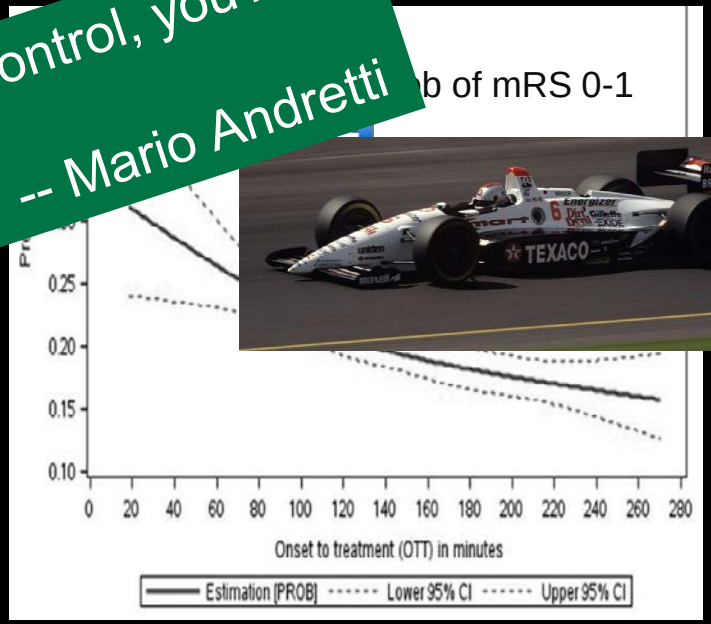


"If everything seems under control, you're not going fast enough"

-- Mario Andretti



UCLA Stroke Center

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UCLA Health
Mobile Stroke Unit
Sponsored by Arline & Henry Gluck Foundation
Santa Monica
Fire Department


Health

Dispatcher impression: Stroke

Provider impression: Stroke

NIHSS : 7
LAMS: 3

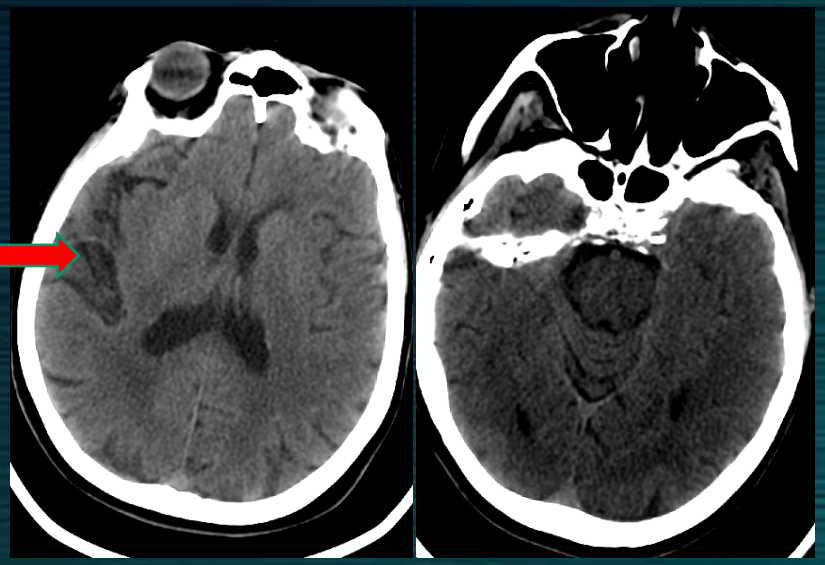
Clinical scenario: 76 year old woman with history of prior TIA (lip numbness & dysarthria 5 month prior), presenting with witnessed acute onset left face/arm weakness, difficulty with ambulation

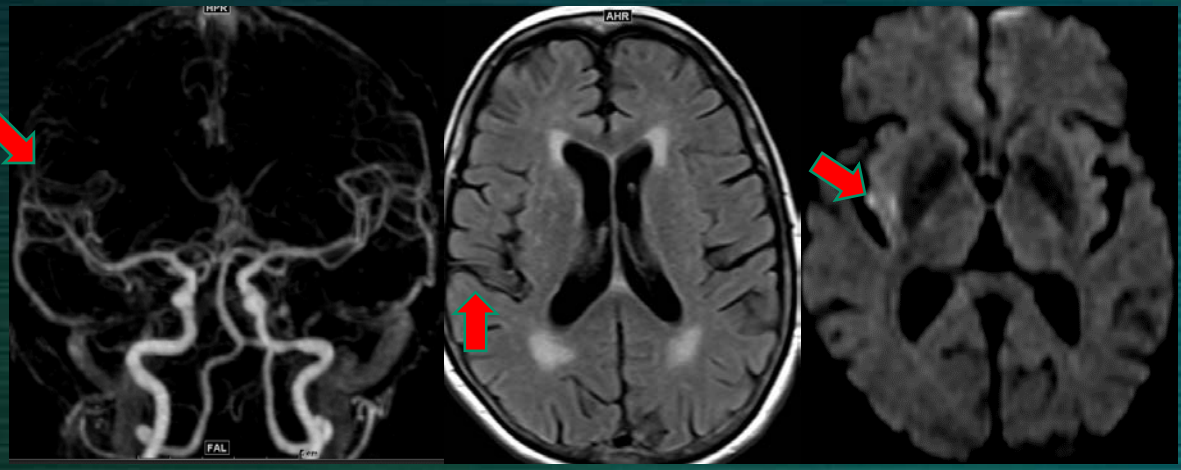
Acute NIHSS 7: left face/arm weakness, numbness, ataxia, dysarthria, sensory

LKWT-to-Tx time: 45 min
MSU admission-to-CT time: 5 min
MSU admission-to-needle time: 19 min

24 hr NIHSS 1: mild sensory deficit in left arm

MSU CT

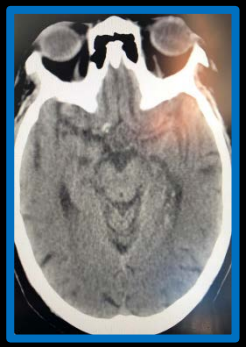


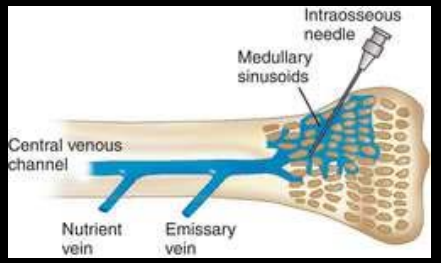


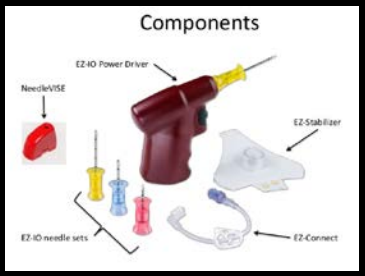
Hospital MRI

First Prehospital Interosseus Administration of tPA for Ischemic Stroke

- 94 yo woman
- H/o afib, on aspirin
- Acute global aphasia, right hemiparesis
  - » NIHSS 16
- Initial IV access attempts unsuccessful
- No adverse effects (but no improvement)







~~First~~ Second Prehospital Interosseus Administration of tPA for Ischemic Stroke

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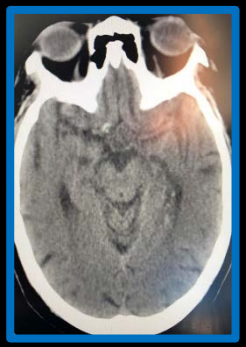

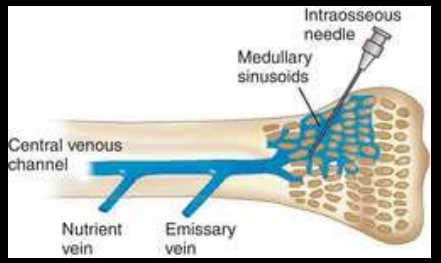

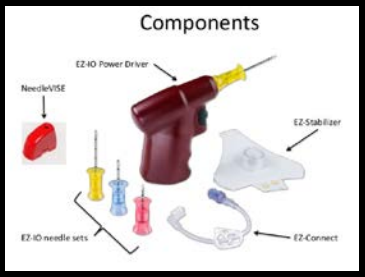

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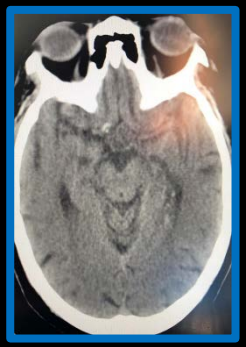

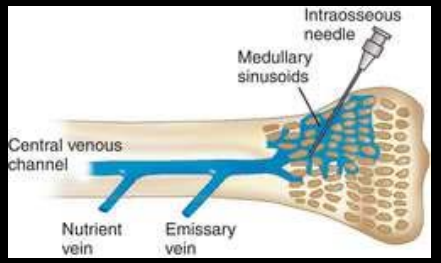

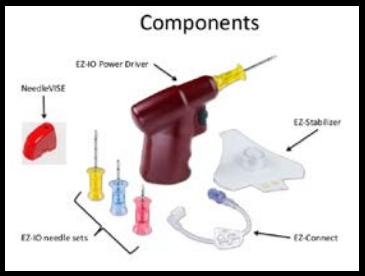

--Series of 3 cases: Bowry et al, Prehosp Emerg Care 2018

BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU) Trial

- Cluster-control RCT
  - » 5 EMS Regions USA
  - » 1 week on, 1 week off
  - » Patients
    - 6000 assessed
    - 1200 enrolled
      - » 700 fully tPA eligible
- Key entry criteria
  - » LKW within 4.5h prior to ambulance evaluation
  - » tPA eligible prior to CT/labs
- Outcome: Utility-weighted mRS at 90d
- Timeline: 2014-2021

Future Technology / Trials?

Helicopter MSU

Mobile Neurointervention Suite

Population and Resources

UCLA Stroke Center

Population and Resources

UCLA Stroke Center