Treatment in the Golden Hour

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Disclosure Information

GWTG

- Disclosures
  - SAB: Talecris, Ev3, CoAxia, Concentric, Ferrer
  - Lecture Honoraria: Ferrer, Boehringer Ingelheim (secondary prevention),
  - UCLA payments for enrolled patients: NIH CLEAR-ER, IMS 3, MR RESCUE Trials, Lundbeck, Concentric
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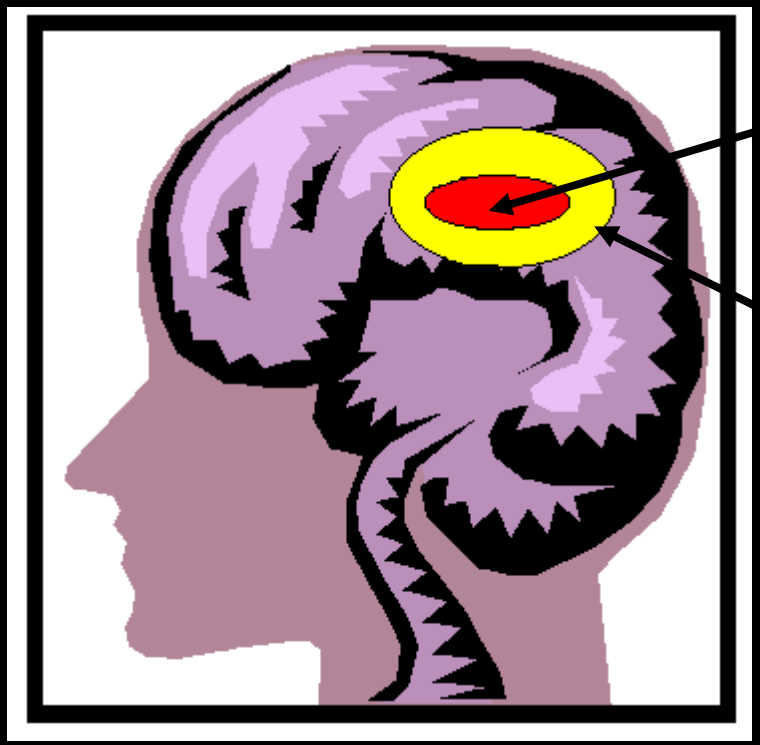
Talk Outline: Treatment in the Golden Hour

- Physiology
  - » Evidence that “time is brain”
- The Clinical Present
  - » Presenting features and lytic therapy in under 1 hour arriving patients in the United States
- A Potential Future
  - » Neuroprotective therapy in the field

The Ischemic Penumbra



Core Infarct

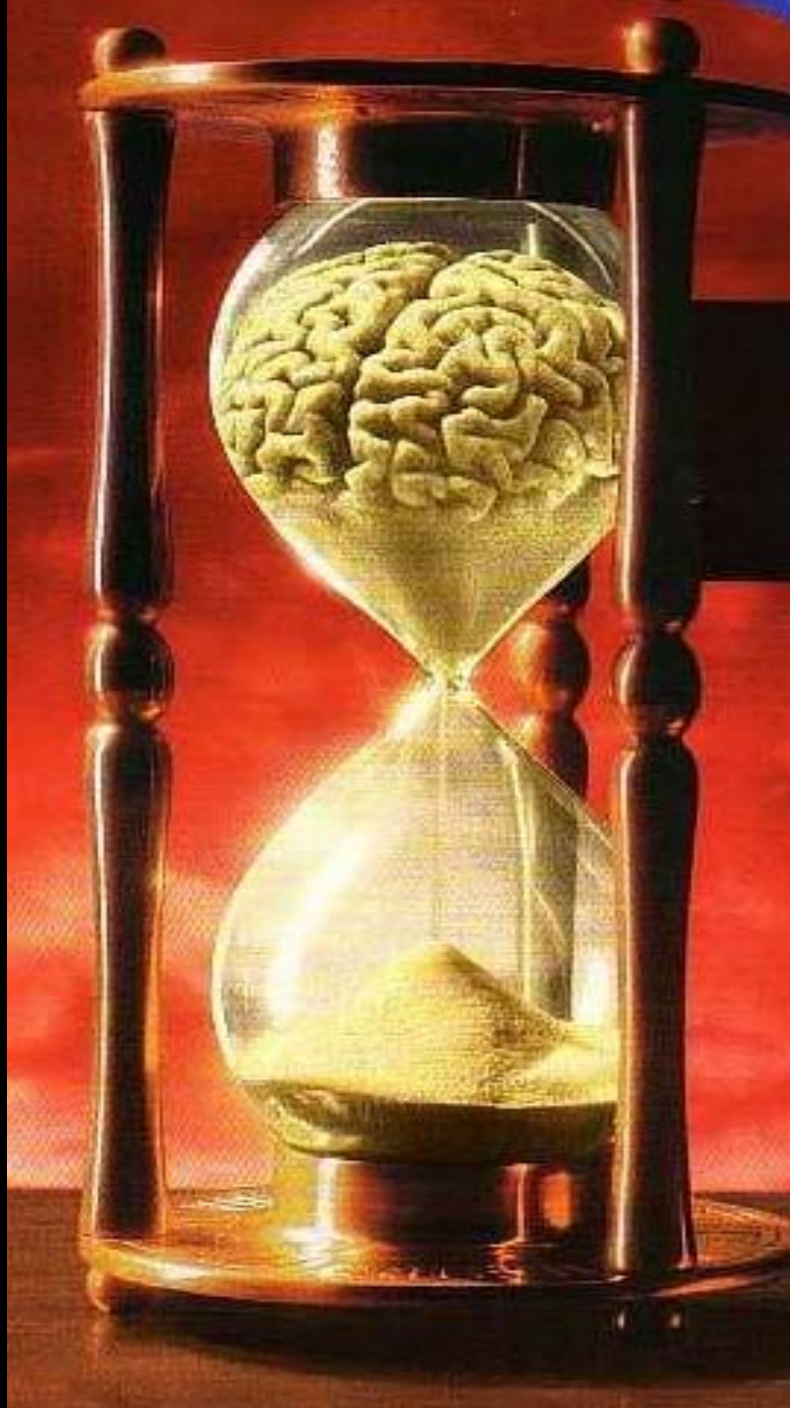
Ischemic Penumbra:

zone of salvageable tissue surrounding core infarct

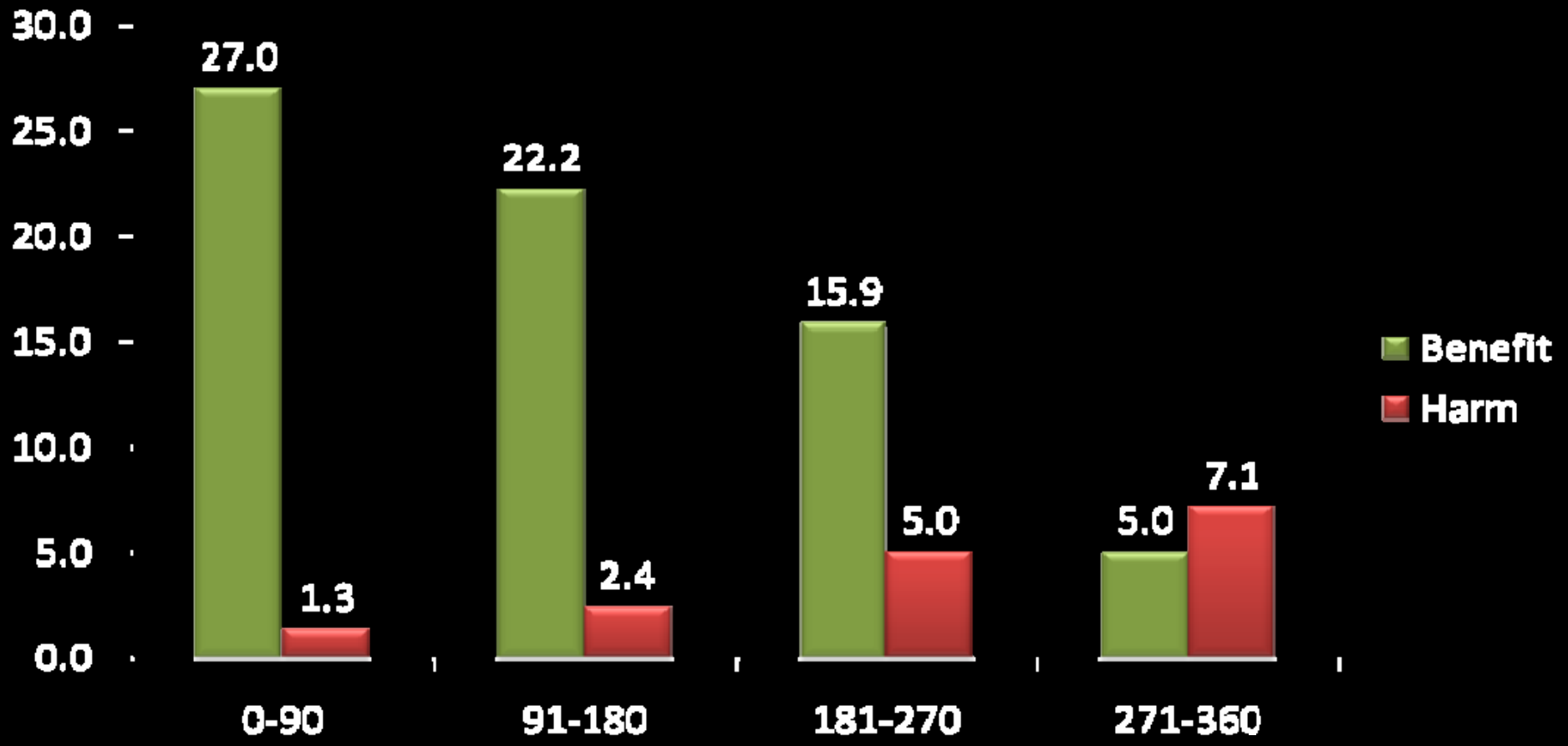
In a typical acute ischemic stroke, every minute the brain loses

- 1.9 million neurons
- 14 billion synapses
- 7.5 miles myelinated fibers

-- Saver, Stroke 2006



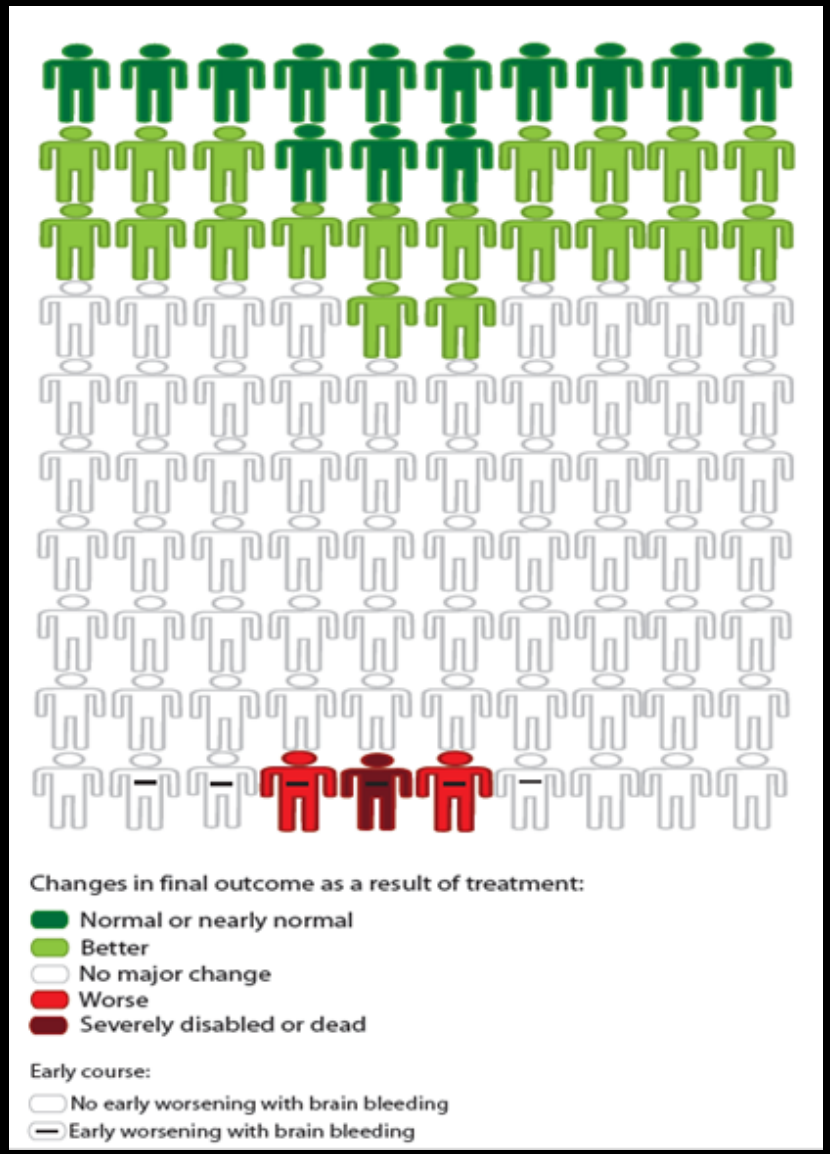
Number of Patients Who Benefit and Are Harmed per 100 Patients Treated in Each Time Window



--Lansberg et al, Stroke 2009

IV TPA Under 3 Hours – Patient Education

- Joint AHA-AAN-ACEP text tool to educate patients and families
- UCLA icon array tool based on AHA-AAN-ACEP



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Stroke and the Golden Hour

- 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

GWTG

The Golden Hour and Acute Brain Ischemia: Presenting Features and Lytic Therapy in Over 30,000 Patients Arriving within 60 Minutes of Onset at GWTG-S Hospitals

Jeffrey L Saver, Eric E Smith, Adrian Hernandez, DaiWai Olson, Xin Zhao, Lee Schwamm

Background/Purpose

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- The benefit of intravenous thrombolytic therapy in acute brain ischemia is strongly time dependent
- Therapeutic yield is maximal in the first minutes after symptom onset and declines steadily during the first 3 hours
  - 1.9 million neurons lost per minute
  - Every 10 minute delay in delivery of TPA, 1 fewer patient has improved outcome
- BAC/AHA/NIH recommendation: door to needle (DTN) time < 60 minutes
- Patients who present to hospital within the first 60 minutes of onset (the “golden hour”) have the greatest opportunity to benefit from recanalization therapy, but hyperacute-arriving patients and their treatment have not previously been well-characterized

Methods: GWTG-S

GWTG

- National acute stroke registry
  - Made available to any US hospital in April 2003
- Trained hospital personnel instructed to ascertain consecutive acute IS, TIA, and HS admissions
- Case ascertainment prospective, retrospective, or both (hot and cold pursuit)
- Medical record data abstracted using internet-based Patient Management Tool
  - Concurrent and retrospective data collection
  - Predefined logic and range checks, user alerts
- Patient characteristics
  - Demographics, medical hx, initial imaging findings, in hospital treatment and events, discharge treatment, discharge destination
- Hospital level characteristics
  - Bed size, academic vs nonacademic status, volume of stroke discharges, geographical region

Methods: Analysis

- The Get with the Guidelines - Stroke (GWTG-S) database was analyzed to characterize ischemic stroke patients arriving to hospital EDs ≤ 60 minutes compared to > 60 minutes after symptom onset
  - 4.75 year time period: 4/03-12/07
- Group differences in demographics (age, sex), stroke severity, arrival mode(ambulance, private vehicle), door to needle (DTN) time, door to imaging (DTI) time, and outcome destination at discharge were characterized by chi square and t tests

Results: Analysis Sample

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- 905 hospitals, 4.75 years

- 517,792 stroke and TIA patients
  - Not direct to ED arrival (e.g. transfer pts) 106,906
  - ICH, SAH, or TIA 157,738

- 253,148 ischemic stroke patients
  - Exact OTD time not documented 146,224 (57.8%)

<u>106,924 direct arriving ischemic stroke patients with documented OTD time</u>

American Heart Association. | American Stroke Association. Learn and Live.

Results: OTD Times

- 106,924 ischemic stroke patients arrived directly to GWTG-S hospital EDs by ambulance or private vehicle

Onset to Door Times	N	Percent
< 60 mins	30,220	28.3%
61-180 mins	33,858	31.7%
> 180 mins	42,846	40.1%

Among < 60 mins patients, mean onset to door (OTD) time: 39.9 mins (SD 14.8)

Results: Patient Characteristics

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	≤ 1 Hr	1-3 Hrs	> 3 Hrs	P value
Age (SD)	71.5 (14.6)	72.1 (14.3)	70.6 (14.2)	< 0.0001
Sex (Female)	50.8%	52.2%	51.5%	0.002
White, Non-Hispanic	77.3%	77.5%	72.5%	< 0.0001
Black	11.8%	11.9%	15.8%	< 0.0001
Arrival by ambulance	79.0%	72.2%	55.0.%	< 0.0001
NIHSS (median, IQR)	8 (3-16)	6 (2-12)	4 (2-9)	< 0.0001

Results: IV TPA

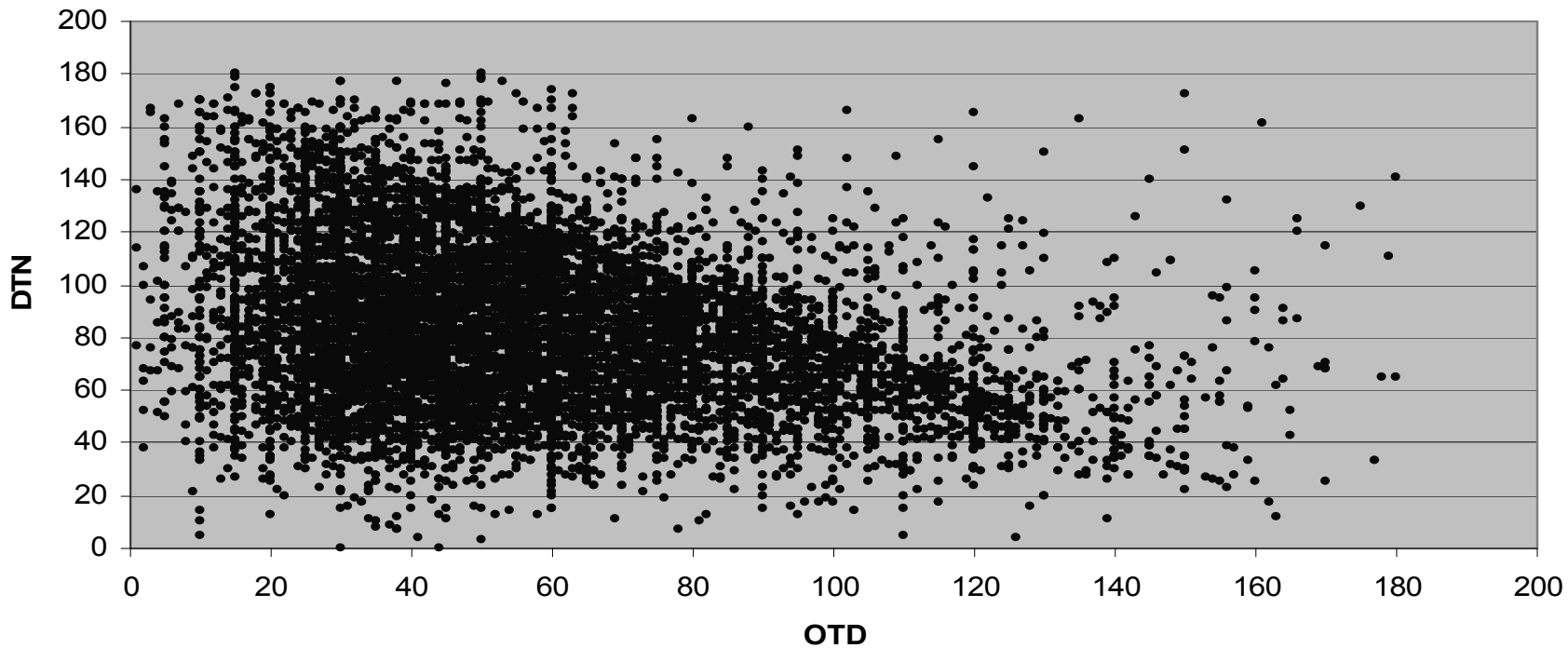
GET WITH THE GUIDELINES GWTG

- IV TPA given to:
  - 12,545 direct ED IS patients
  - 159 direct ED aborted IS patients (TPA-induced TIA)
  - 11.8% of all direct ED, IS patients with documented OTD
  - 5.0% of all direct ED IS patients
- Mean OTD 56.3 mins, DTN 84.1mins

Onset to Door Times Among IV TPA Patients	N	Percent
< 60 mins	8111	64.7%
61-180 mins	4327	34.5%
> 180 mins	107	0.9%

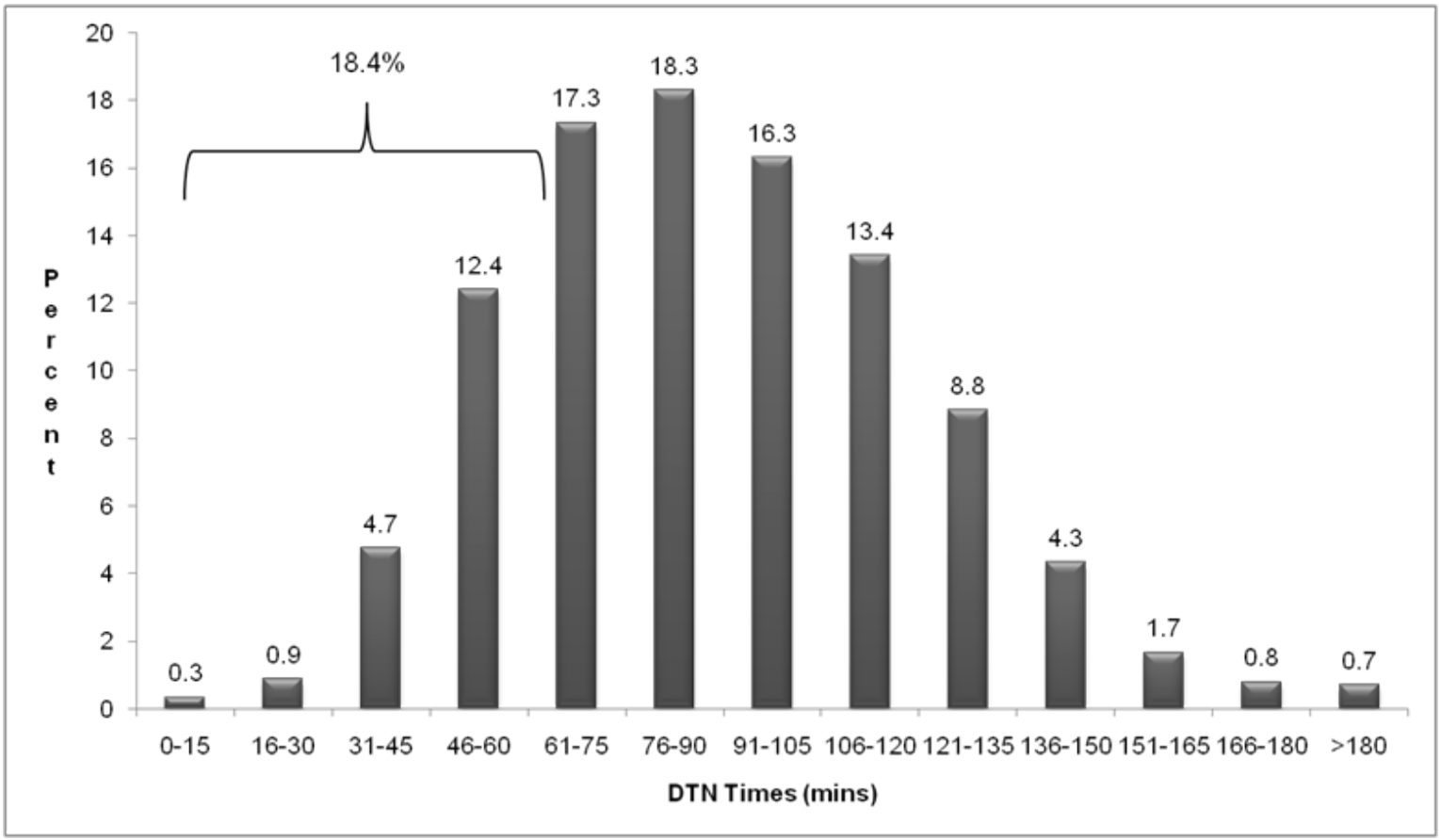
- IV TPA more frequent among golden hour patients than 1-3 hour
  27.1% vs 12.9%, $p < 0.0001$

Results: IV TPA DTN Times



- DTN in all 12,545 IV TPA patients: 86 mins (SD 42)
- Longer DTN in golden hr patients: mean 90.6 v 76.7 mins, $p < 0.0001$
- Inverse relation OTD – DTN times: $r = -0.30$

Results: DTN Time among Golden Hour Patients



Results: Target DTN Time ≤ 60 Minutes I

GWTG

- Target DTN ≤ 60 mins achieved in 18.3% of golden hour-arriving patients
- Modest increase in proportion of patients with target DTN times by calendar year

Year	Proportion with DTN ≤ 60 mins
2003	12.8%
2004	15.9%
2005	18.9%
2006	17.8%
2007	19.5%

Absolute increase 1.2% per year, p=.027

Results: Target DTN Time ≤ 60 Minutes II

GWTG

- No substantial increase in proportion of patients with target DTN times duration of hospital participation in GWTG-S

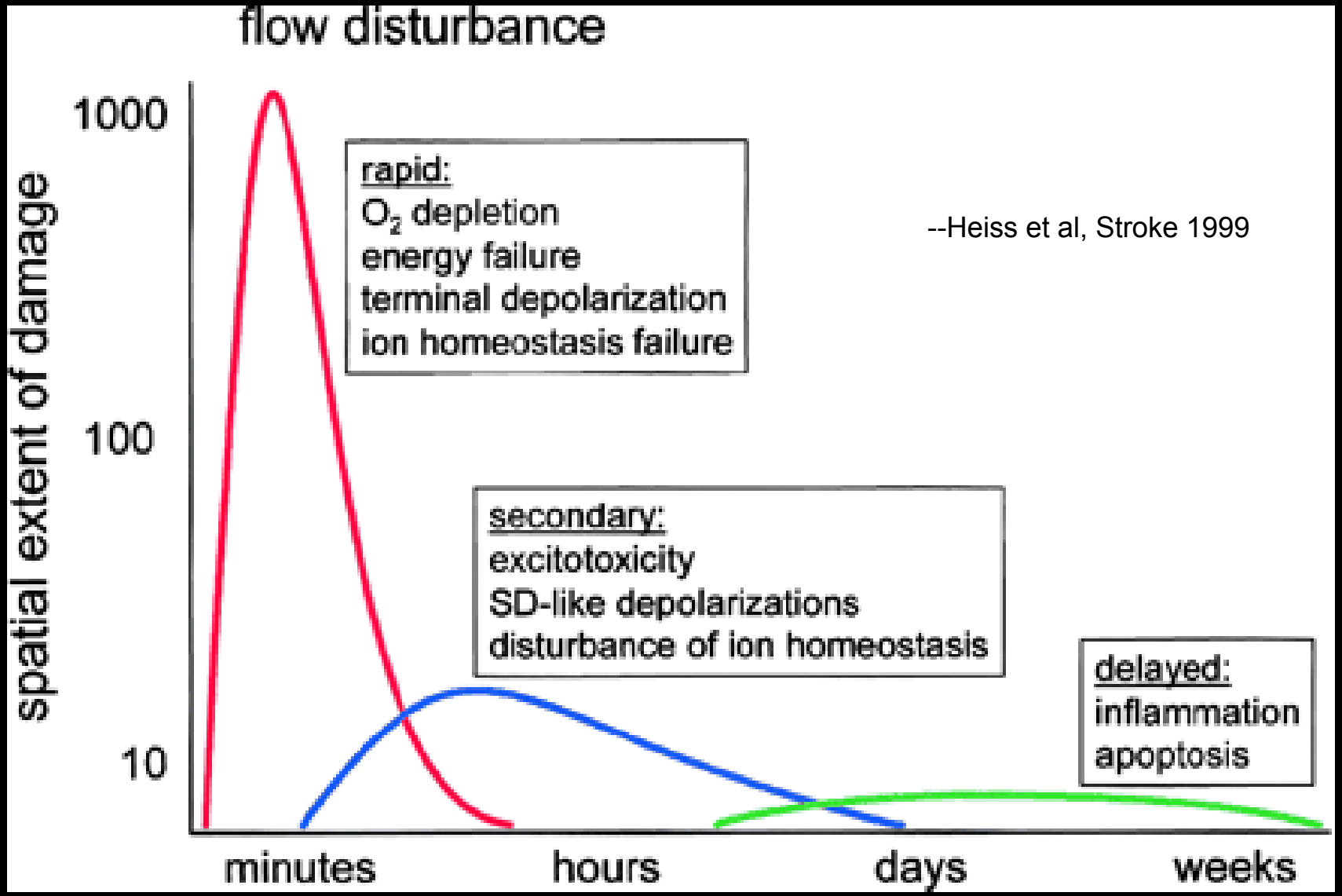
Year Participating in GWTG-S	Proportion with DTN ≤ 60 mins
1	18.0%
2	18.5%
3	18.4%
4	19.0%
5	18.9%

p = 0.65

Conclusions

- Twelve percent of ischemic stroke patients presenting to GWTG-S hospital EDs arrive within 1 hour of documented onset time
  - Projected nationally, this indicates that ~74,000 acute ischemic stroke patients present within 60 minutes of onset to US hospital EDs each year
- Golden hour-arriving patients receive thrombolytic therapy more frequently and earlier than late arrivers
- Target door to needle times ≤ 60 minutes are achieved in fewer than one-fifth of golden hour-arriving patients
  - Improving national trend over time, not related to GWTG-S participation
- These findings support:
  - Public education efforts to increase the proportion of patients arriving within the first 30-60 minutes after stroke onset
  - Hospital performance improvement activities to shorten door to needle times in patients who arrive within the “golden hour”

“The Ischemic Cascade”



--Heiss et al, Stroke 1999

Classification of Neuroprotective Agents

- Modulators of Excitatory Amino Acids
- Modulators of Calcium Influx
- Metabolic Activators
- Anti-edema Agents
- Inhibitors of Leukocyte Adhesion
- Free Radical Scavengers and Anti-Oxidants
- Promotors of Membrane Repair
- Unknown or Other Mechanism(s)

Trials of Neuroprotective Agents for Stroke, 1955-2000

Neuroprotective agents tested	49
RCTs performed	114
Patients enrolled	21,445
Neuroprotective agents approved	0

Time windows: 4-48 hours

-- Kidwell, Liebeskind, Starkman, Saver, Stroke 2001

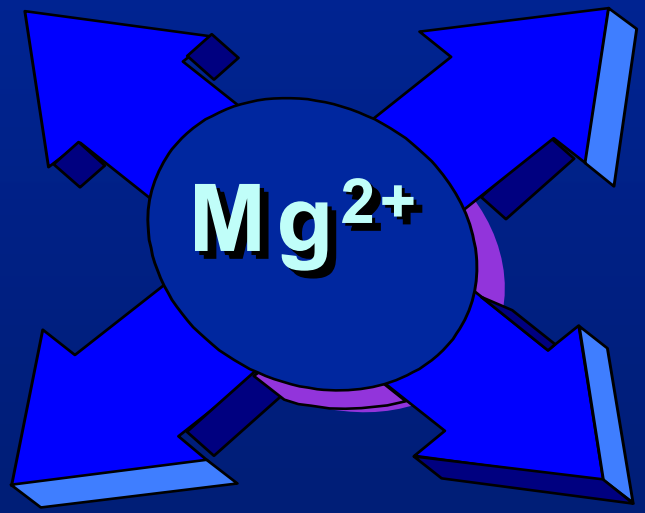
IMAGES

Intravenous MAGnesium Efficacy in Stroke

Possible Therapeutic Effects of Magnesium in Stroke

Vascular

- Increased Cardiac Output
- Increased Regional CBF



- NMDA Ion Channel Blockade
- Ca^{2+} Channel Blockade
- Enhanced ATP Recovery

Neuronal

Prehospital Stroke Neuroprotective Trials: Distinctive Methodologic Aspects

- Diagnosing stroke in the field
  - LAPSS
- Rating stroke pretreatment severity
  - LAMS
- Eliciting consent
  - Cellular MD
- Characterizing early, field response to therapy
  - PGIC

Remote Investigator Elicitation of Consent

- Explicit consent obtained in the field
  - » Patient or legally authorized representative on scene
- Written consent form in vehicle
- Cell phone in each ambulance
- VOIP simultaneous ring connection to 4 on call enrolling investigators
- Paramedic provides consent provider with written consent form and connects by cell phone to MD
- MD investigator elicits consent by phone

The Field Administration of Stroke Treatment – Magnesium (FAST-MAG) Pilot Trial

UCLA Stroke Center

FAST-MAG Pilot Trial Results

- 20 patients enrolled
- Age 74, range 44-92
- 10 female, 10 male
- 80% ischemic, 20% ICH

Primary Endpoint
Time On Scene to Start of Infusion

	Time (±SD)
FAST-MAG (n=20)	23 min (±12)
Prior Trials (n=26)	141 min (± 70)

p < 0.0001

Time Savings: 1 hr 58 min

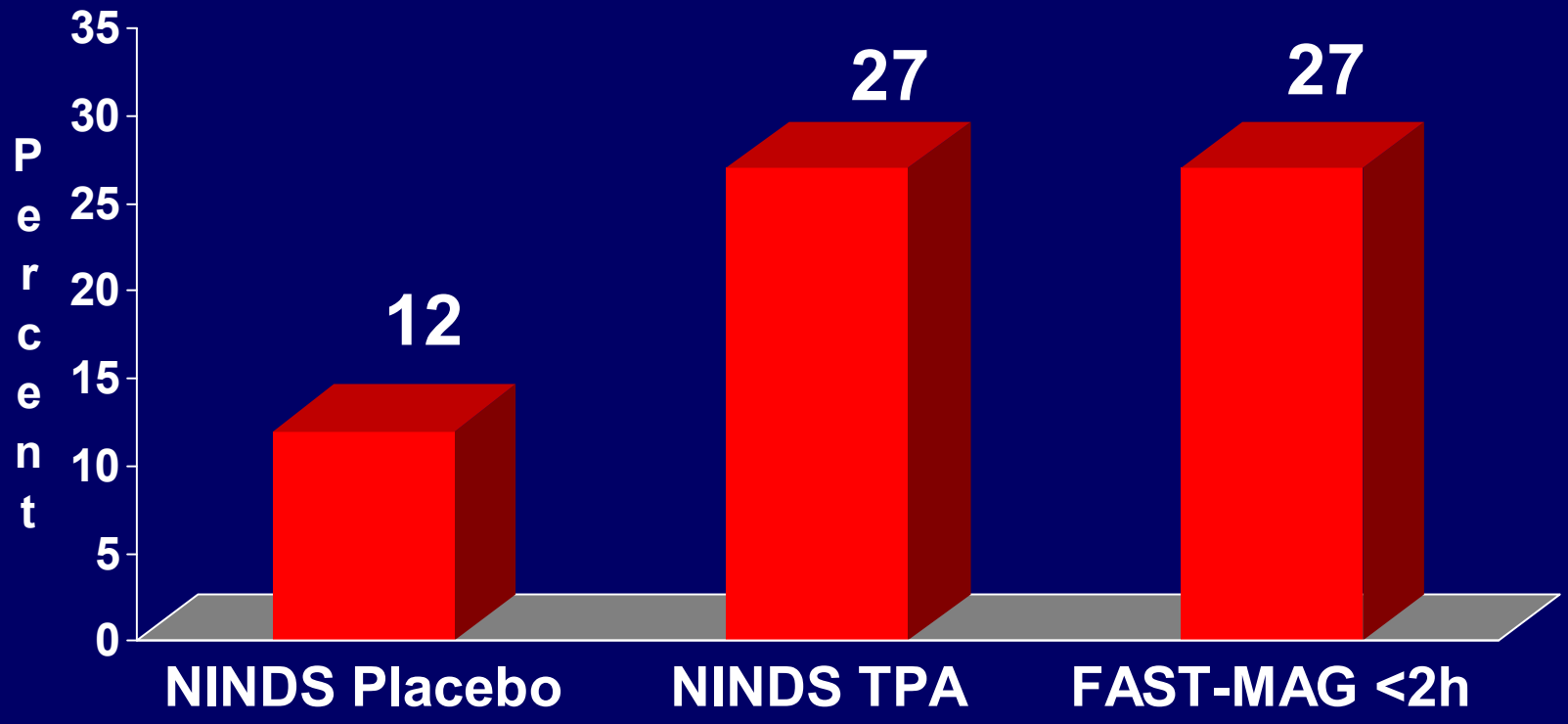
FAST-MAG Pilot Trial
Time On Scene to ED Arrival

	Time (±SD)
FAST-MAG (n=20)	36.7 min (±10.0)
Prior Trials (n=26)	35.0 min (± 20.1)

p = 0.73

Dramatic Early Recovery

Improved Completely or ≥ 10 NIHSS Points at 24 hours



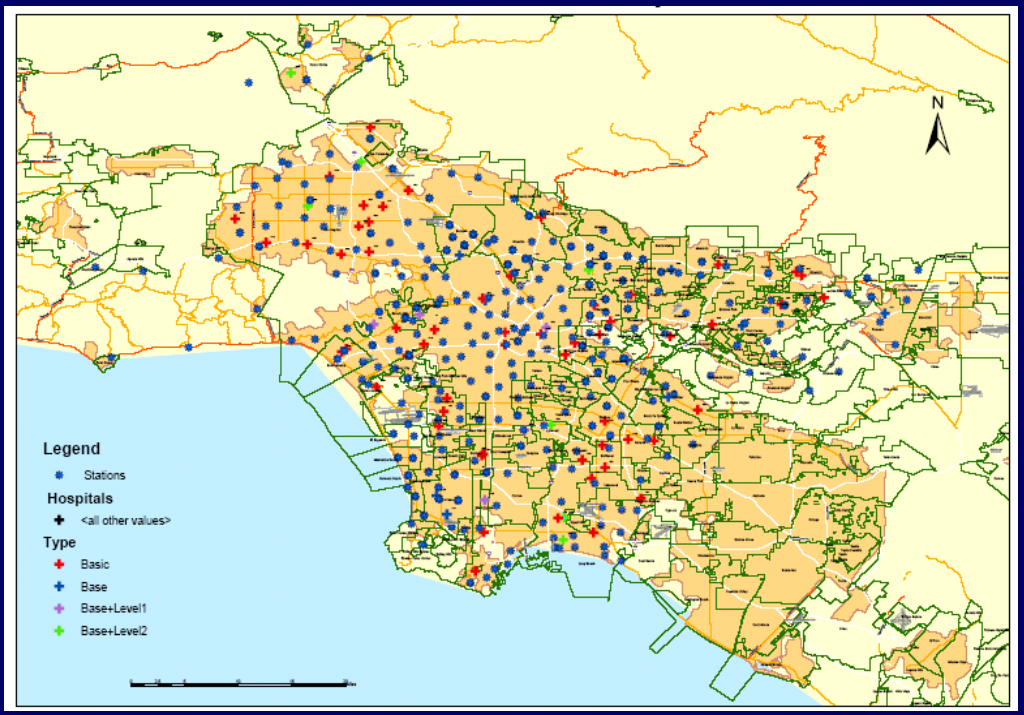
The Field Administration of Stroke Therapy – Magnesium (FAST-MAG) Phase III Trial

UCLA Stroke Center

Field Administration of Stroke Treatment – Magnesium (FAST-MAG) Trial

- Placebo-controlled, double-blind, randomized
- Multicenter, single region
  - 69 hospitals, Los Angeles County
- 4 gm Mg field, 16 gm Mg maintenance x 24h
- 1298 patients
- NIH Grant 4 years, enrollment period 3.5 years
- Primary endpoint: Rankin Scale

FAST-MAG Trial Setting and Participating Sites



- Los Angeles County
- Ethnically diverse population 10.1 million
- 55 receiving hospitals
- 228 rescue ambulances
- 2200 paramedics
- > 380 emergency physicians
- >100 neurologists, neurosurgeons

•Supported by NIH-NINDS

FAST-MAG

Patient Characteristics (First 853 of planned 1298 patients)

Age	70 (range 41-92)
Female	40%
Index Event Diagnosis	
Cerebral ischemia	73%
Intracerebral hemorrhage	24%
Stroke Mimic	3%
Stroke Severity	
LAMS (prehospital)	4.0 (range 1-5)
NIHSS (hospital arrival, after Rx start)	9.0 (range 0-40)

•Supported by NIH-NINDS

FAST-MAG

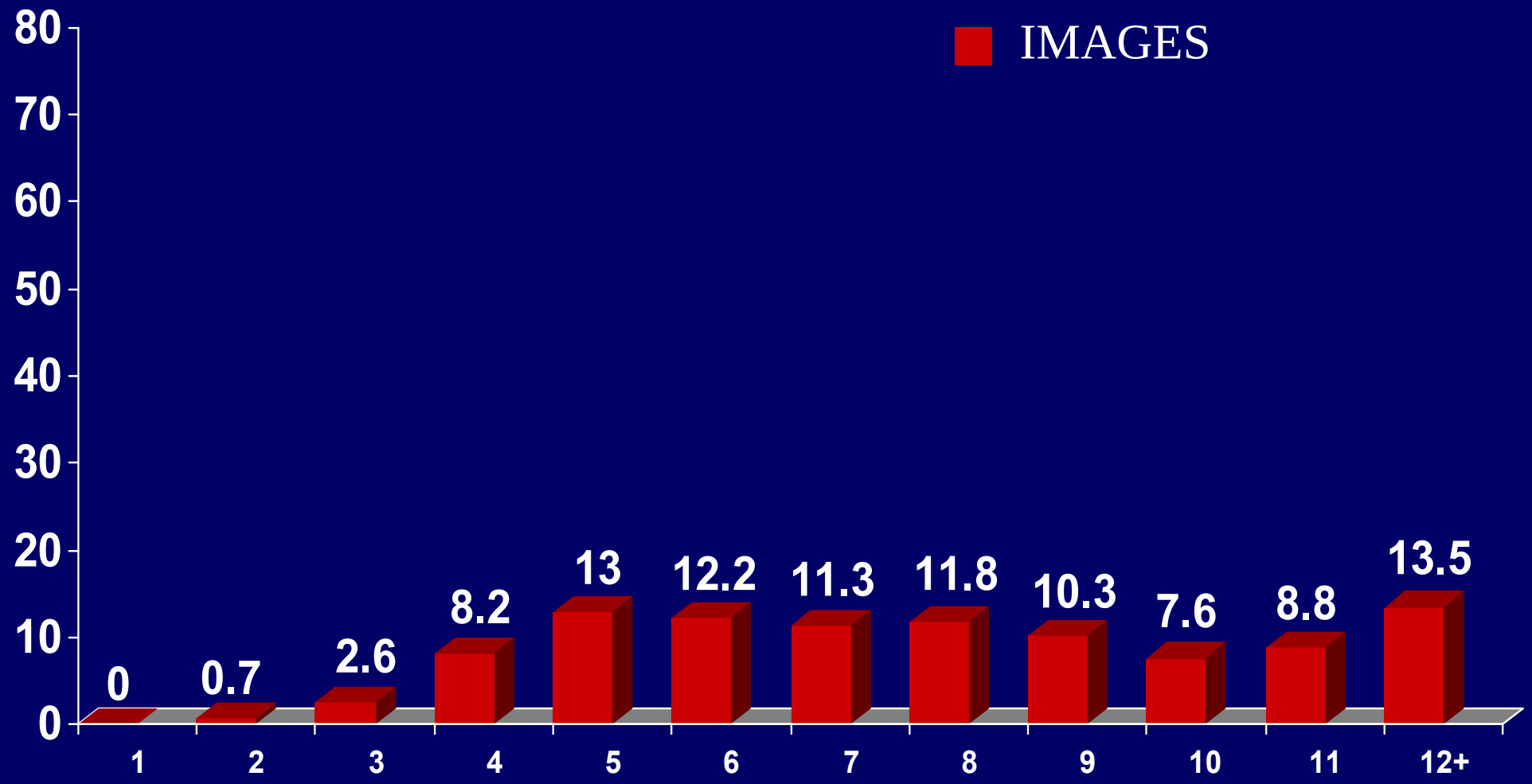
Key Treatment Intervals (n=853)

Stroke onset to study drug (median)	46 mins
Paramedic arrival on scene to drug (mean)	25 mins
Paramedic arrival on scene to ED (mean)	35 mins
Treated within 1 hour of onset	70%
Treated 1- 2 hr after onset	24%

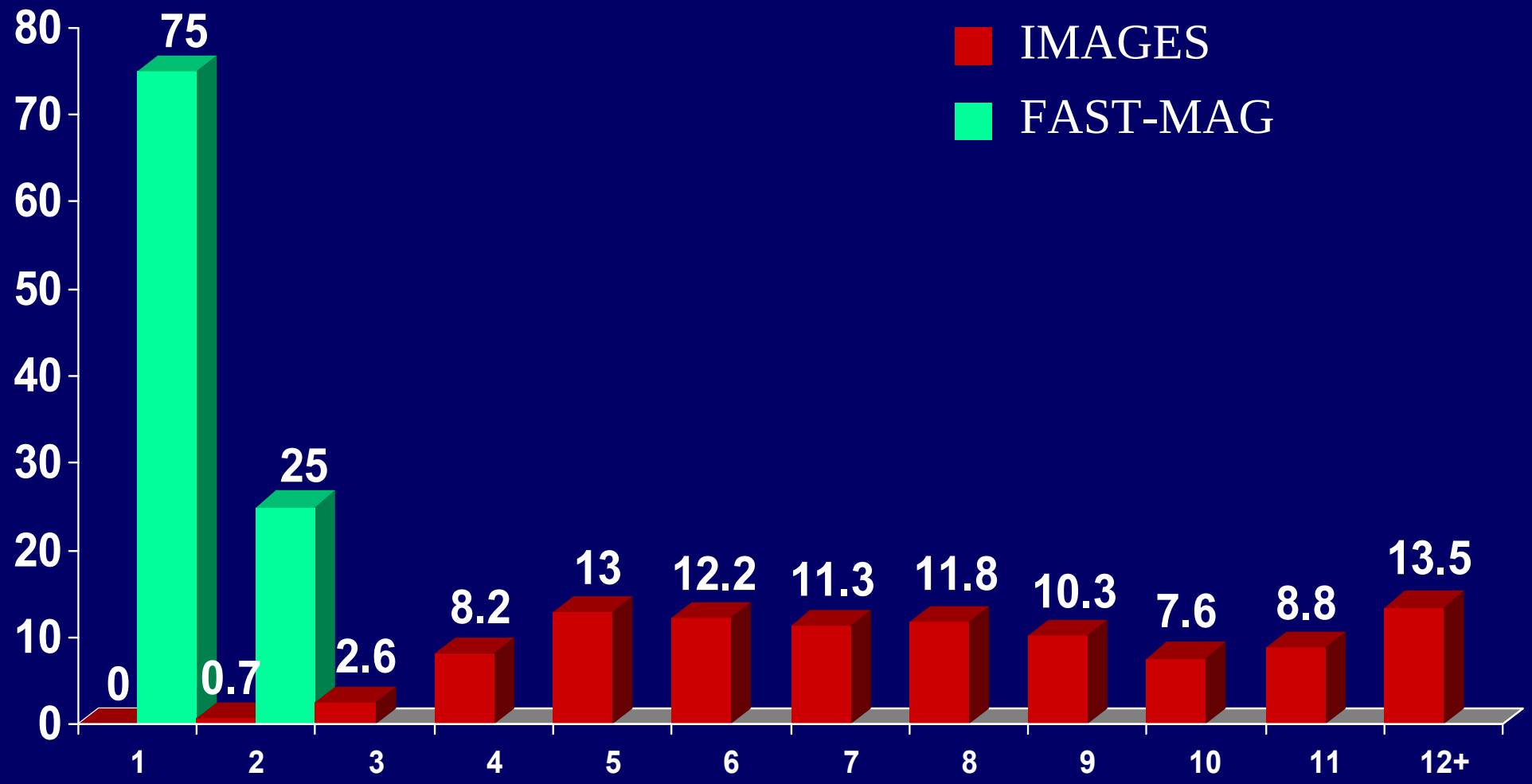
•Supported by NIH-NINDS

FAST-MAG

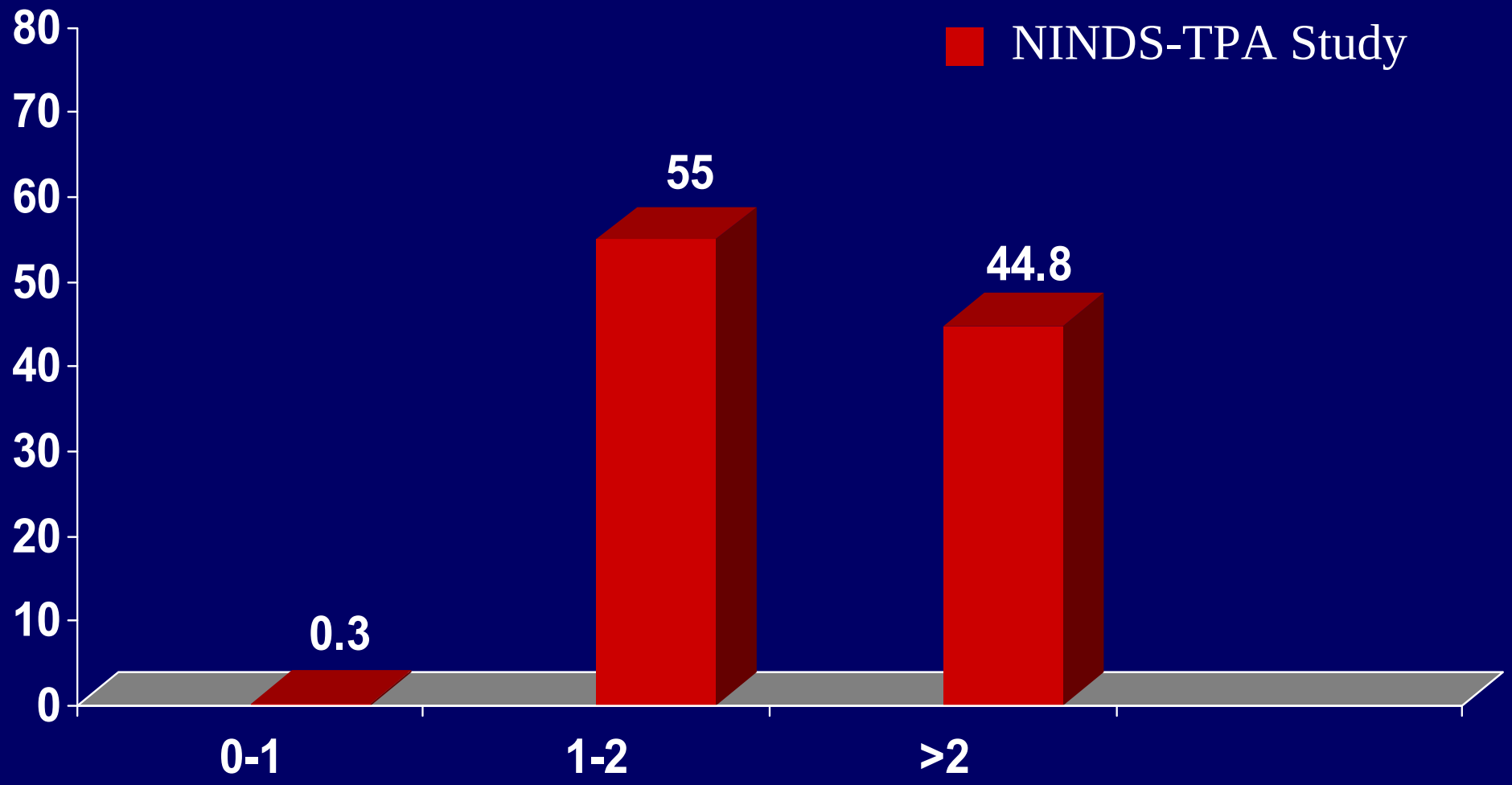
IMAGES Trial Time to Treatment



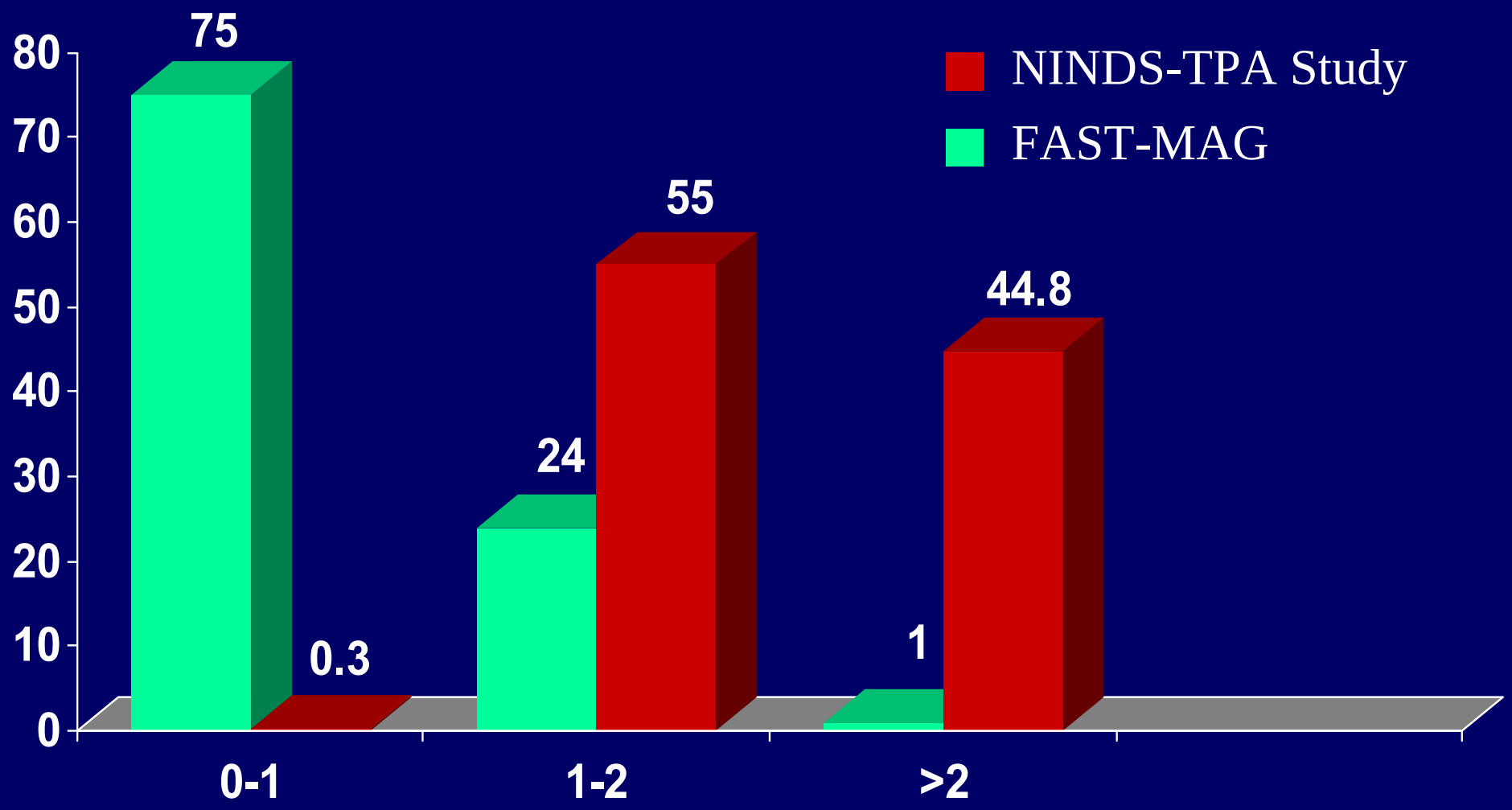
FAST-MAG vs IMAGES
Time to Treatment



NINDS-TPA Study Time to Treatment



NINDS-TPA Study Time to Treatment



FAST-MAG Innovations

- First “golden hour” (<1 hr) stroke treatment trial
- First acute (<3 hr) neuroprotective stroke treatment trial
- First trial of neuroprotective drugs before recanalization therapies
- First prehospital stroke RCT
- First prehospital RCT for any condition employing physician-elicited informed consent

Conclusions: Treatment in the Golden Hour

- Diagnosis and treatment in the first hour after onset offers the greatest opportunity for brain rescue in stroke patients
- Many patients currently present to EDs in the golden hour, with opportunities for more efficient management
- Field initiation of neuroprotective therapy is a promising strategy for treating more patients in the “golden hour”