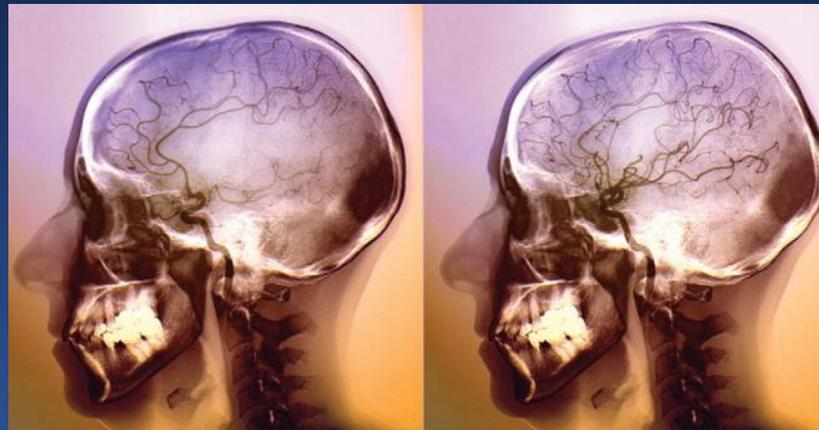


Cerebrovascular Reperfusion: What Do We Have in Common?

Edward Jauch, MD MS



Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant / Research Support

- Affiliations

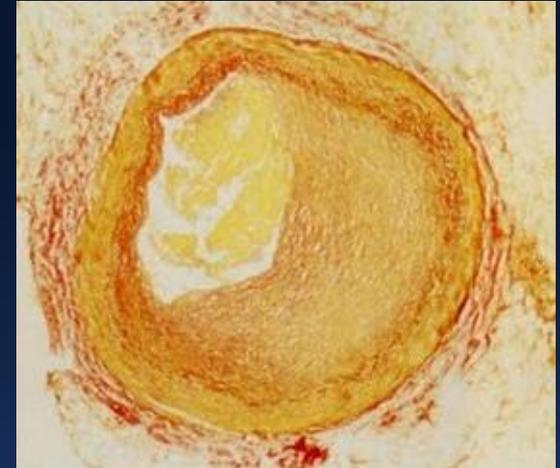
Company

- NIH / NINDS Research funding
FAST-MAG DSMB
- STOP-IT Study Novo Nordisk (drug in kind)
- PRISMS Study Genentech
- POSITIVE Study Covidiene, Stryker,
Penumbra
- BASE Study Ischemia Care

- Medical University of South Carolina
- American Heart Association
Past president, Stroke Council
Guidelines writing group chair
ACLS Stroke writing group chair

Current State of Stroke

- Growing global epidemic paralleling increase in cardiovascular disease
 - Share same risk factors
 - Similar need for reperfusion
 - A regional systems approach key to triaging patients to the level of necessary care
 - Stroke care has lagged STEMI care by decades



Phases of AMI Treatment

- Phase 1 1912 – 1961
Bed rest, expectant treatment
- Phase 2 1961 – 1974
Coronary care units
- Phase 3 1975 – present
Myocardial reperfusion
- Phase 4 Future
Reperfusion injury, regeneration

Development of Acute Stroke Treatments

400BC Hippocrates described “apoplexy”

1920s Contrast angiography developed

1950s First carotid endarterectomy performed

1960s Doppler ultrasonography developed.

1970s Development of computerized tomography (CT)

Aspirin shown to prevent stroke

1980s Development of magnetic resonance imaging

Interventional procedures more aggressive

1987 Beginning of NINDS t-PA Pilot trial

1990s Carotid enarterectomy proven to prevent stroke

Development of Acute Stroke Treatments

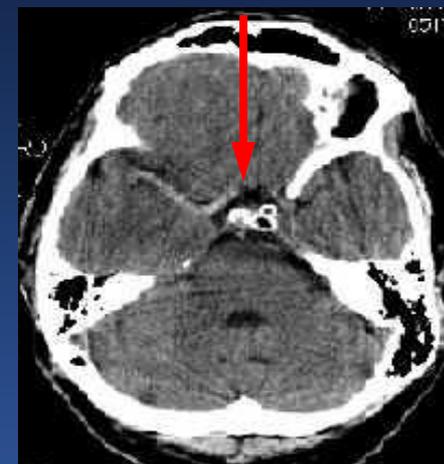
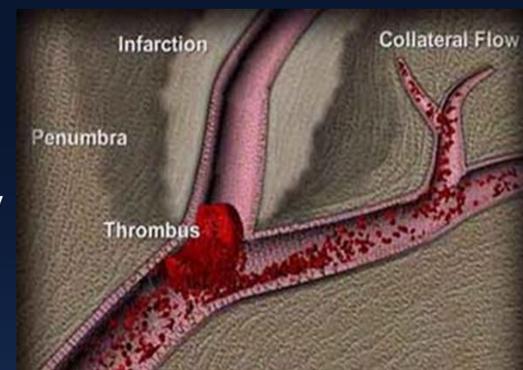
- 1991 Beginning of NINDS t-PA Stroke Trial
- 1993 *Stroke units shown to save lives*
- 1995 Publication of NINDS t-PA Stroke Trial(s); Start of EMS Trial
- 1996 *FDA approval of t-PA for ischemic stroke*
- 1999 Publication of PROACT II Trial
- 2000 *Publication of Primary Stroke Center recommendations*
- 2001 Start of IMS I Trial
- 2004 FDA clearance of Concentric Retriever
Get With the Guidelines – Stroke begins
- 2005 Start of IMS III Trial

Development of Acute Stroke Treatments

- 2006 New DRGs for t-PA and thrombectomy
- 2007 AHA Guidelines for stroke system development
- 2008 *FDA approves thrombectomy device; ECASS III*
Stroke drops from 3rd to 4th leading cause of death
- 2009 AHA guidelines rtPA 3-4 ½ hr window & telemedicine
- 2011 United Nations Summit on NCD, including stroke
AHA guidelines for Comprehensive Stroke Centers
- 2012 JC develops criteria for CSC
Stent retrievers received FDA clearance
- 2013 Large number of studies reporting neutral results

Similar Lessons to STEMI Care

- Reperfusion critical
 - Minimize delay
 - Maximize penumbral salvageability
 - Collateral flow
 - Physiologic optimization
- Time to reperfusion
 - Drives clinical outcomes
 - Affects likelihood of a trial success
 - *Should* drive all system development



Unique Features in Stroke

- Diagnostic challenge
 - No ECG, no troponin, no echo
 - Diagnosis of exclusion
- Clots vary
 - Source either embolic or *in situ* thrombotic
 - Clot size and location highly variable
 - Clot composition complex
 - Extremely tight but variable reperfusion window
 - Disability primary outcome (vs mortality)

Time Dependent Benefit of Reperfusion Therapy

IV rt-PA for Stroke

STEMI Reperfusion

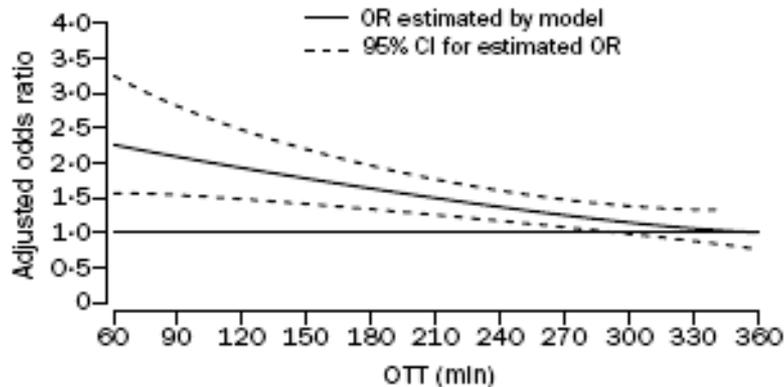
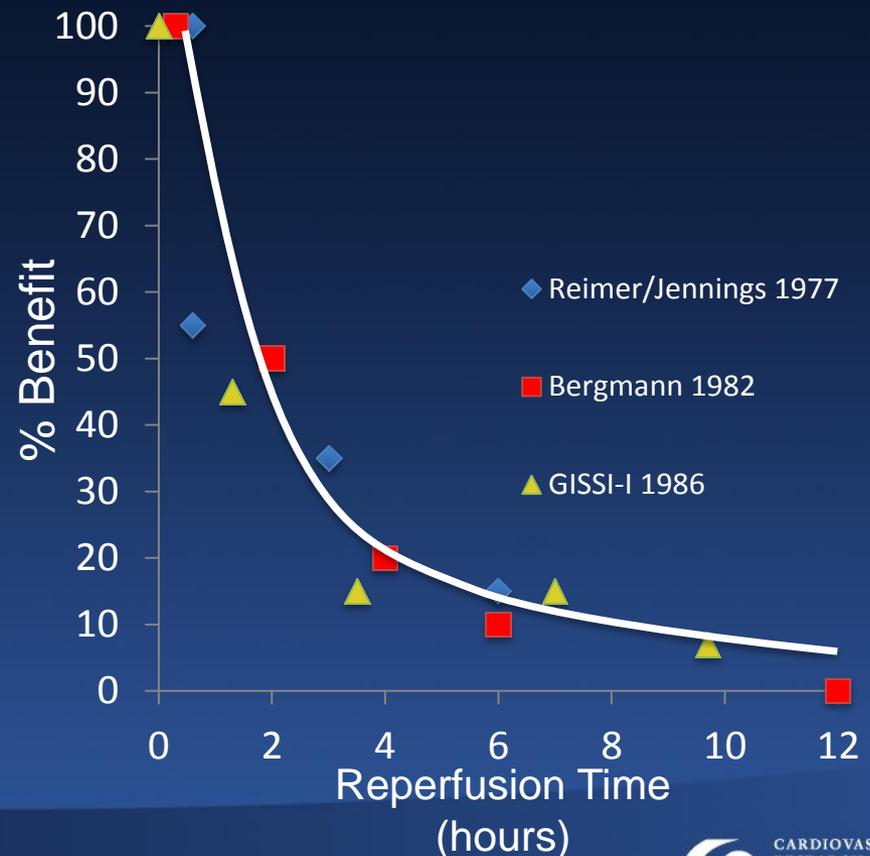
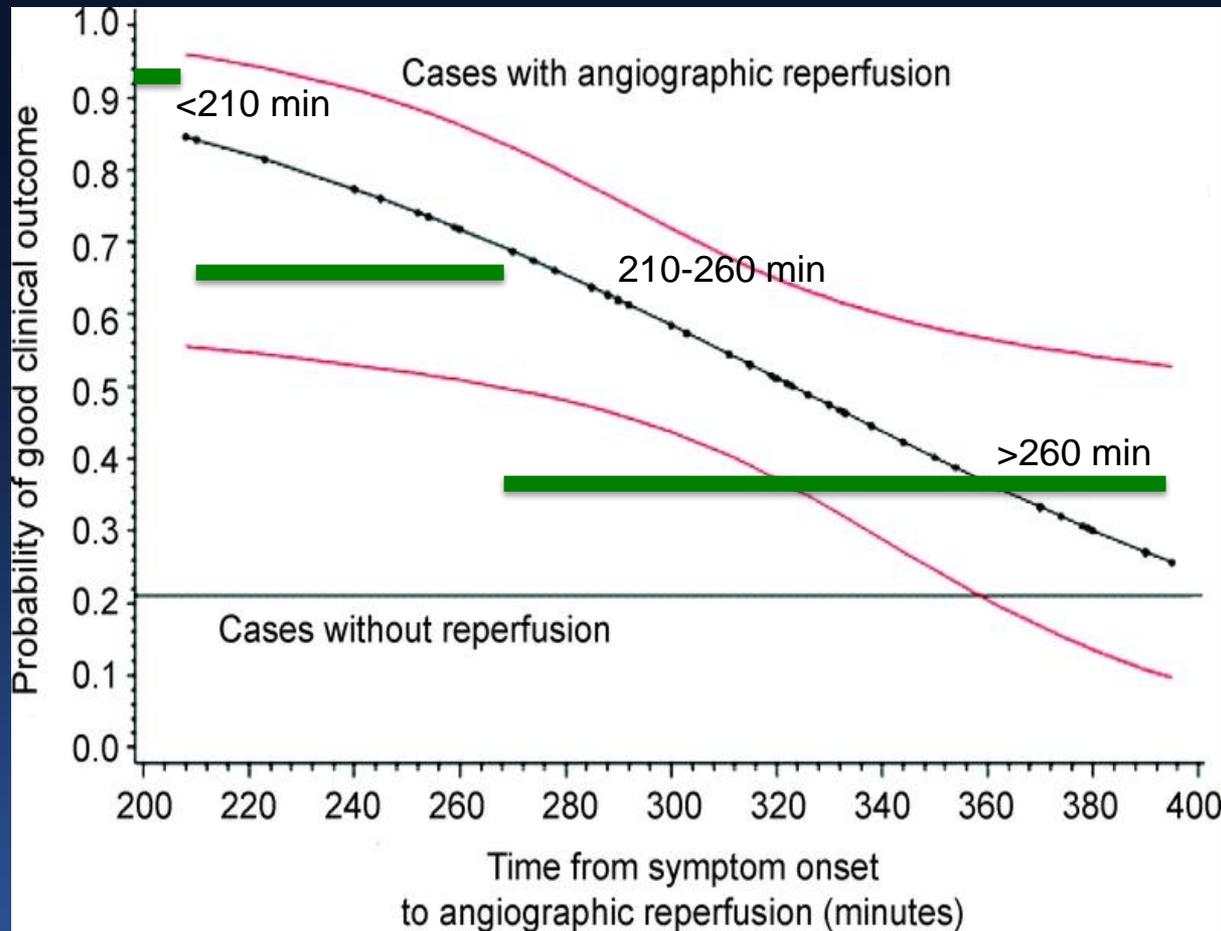


Figure 3: **Model estimating odds ratio for favourable outcome at 3 months in rt-PA-treated patients compared with controls by OTT**

Adjusted for age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS measurement.

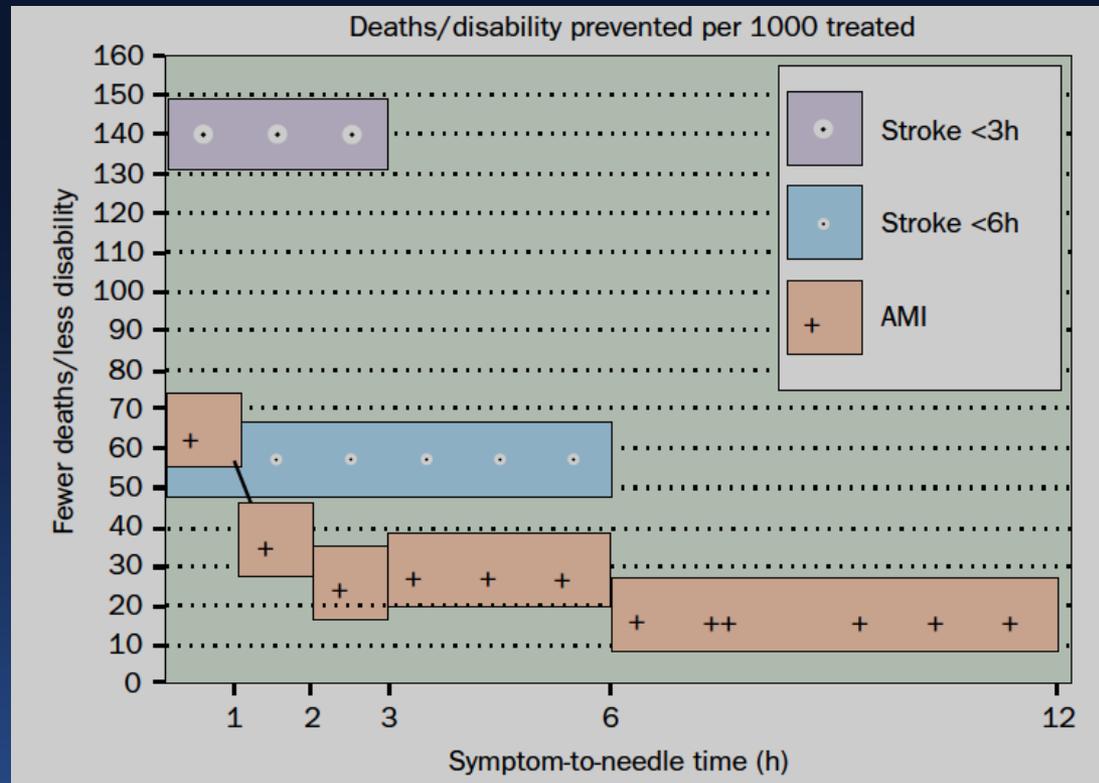


Time to Reperfusion: IA Treatment



Impact of Time on Outcome

Comparison of the relative efficacies of thrombolysis in AMI and acute ischemic stroke (with endpoints of death and death and disability) per 1000 patients treated.

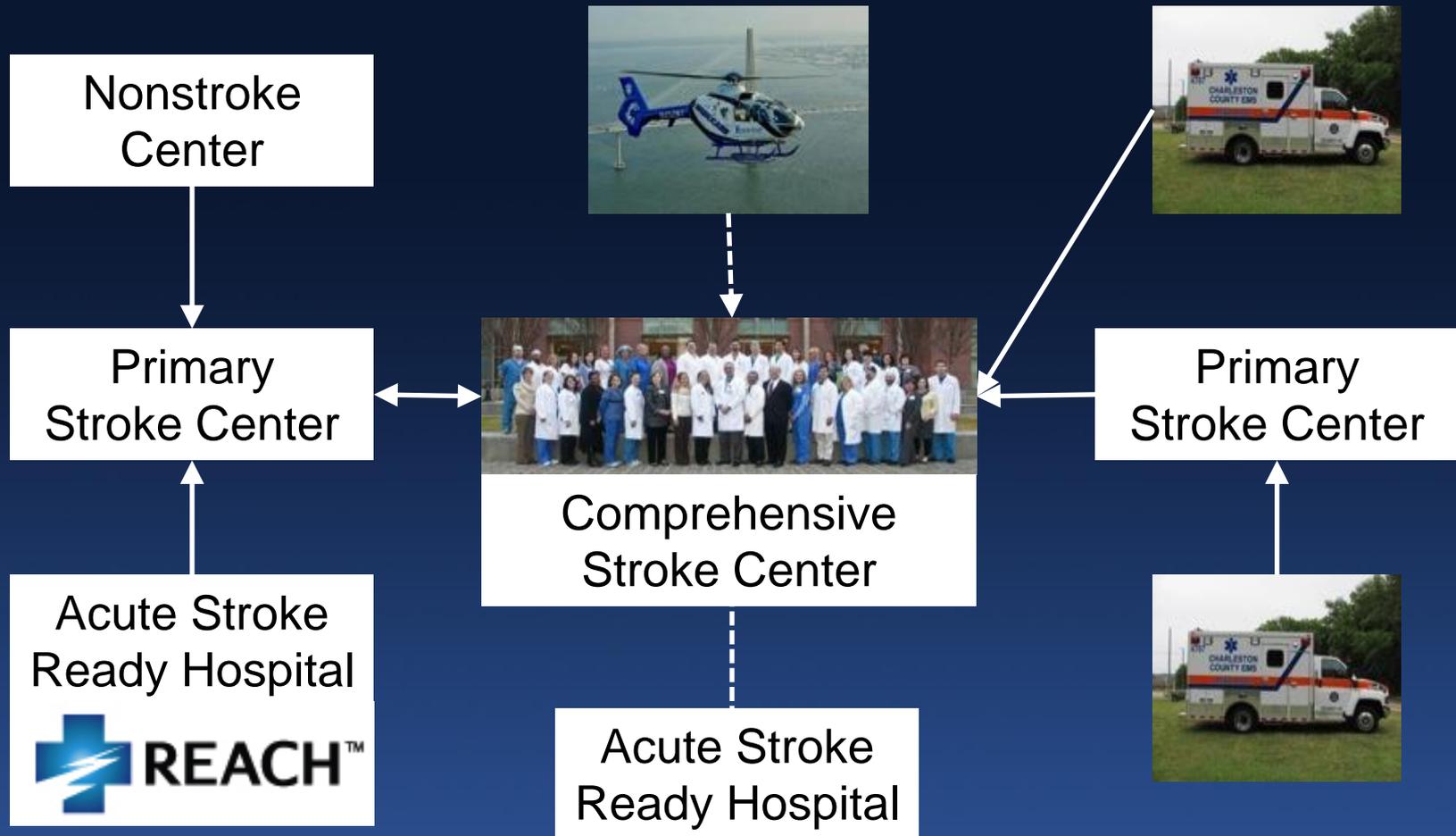


Current Stroke Care

- Public education
- Systems development
- Focus on EMS and Emergency Department care
- Reperfusion drives system
- Specialized hospital-based stroke care
- Early secondary prevention
- Aggressive and early rehabilitation

*sixth annual
sc heart & stroke care alliance:
marking the milestones & mapping the future*

Stroke Systems of Care

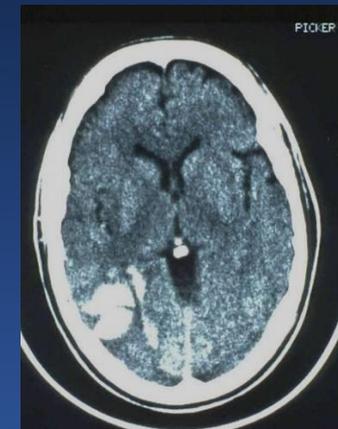


Stroke Chain of Survival



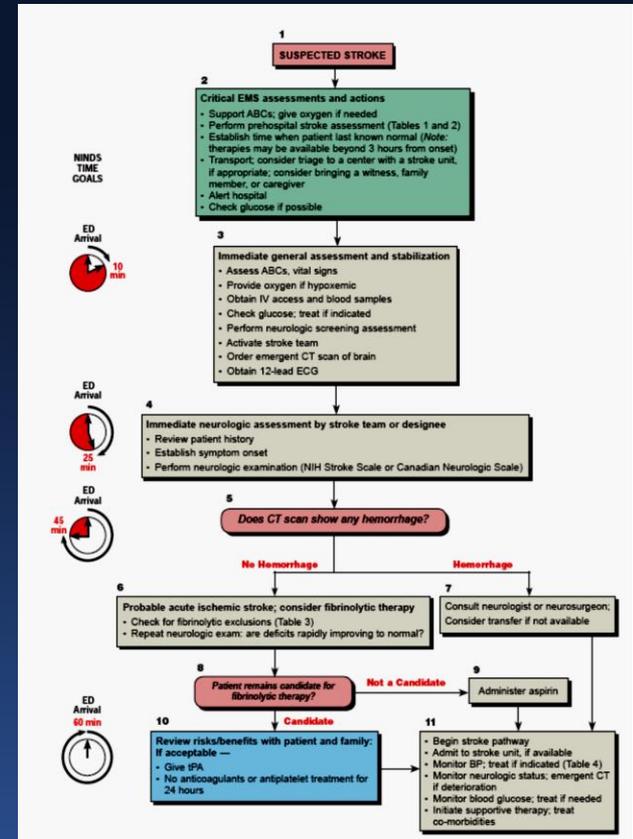
- Detection: Early recognition
- Dispatch: Early EMS activation
- Delivery: Transport & management
- Door: ED triage
- Data: ED evaluation & management
- Decision: Neurology input, therapy selection
- Drug: Thrombolytic, drugs, device
- Disposition: Admission or transfer

Door Emergent Triage Data ED Evaluation (Triad)



Current ACLS Guidelines

- Door-to-MD: 10 minutes
- Door-to-Team: 15 minutes
- Door-to-CT scan: 25 minutes
- Door-to-Drug: 60 minutes
- Door-to-Unit: 3 hours



Decision A Team Approach Drug(s) / Device

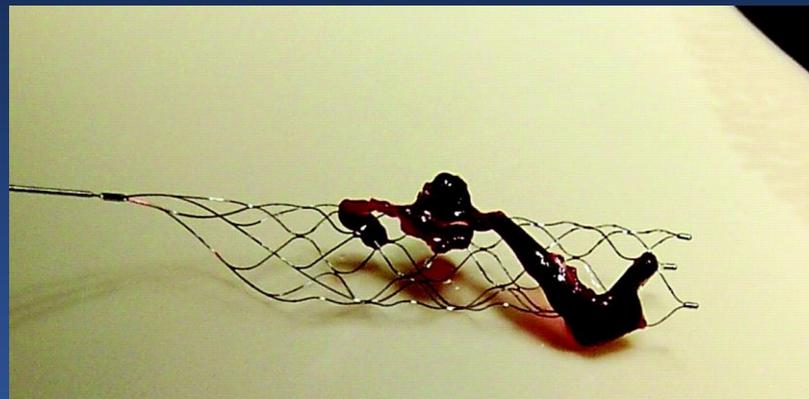
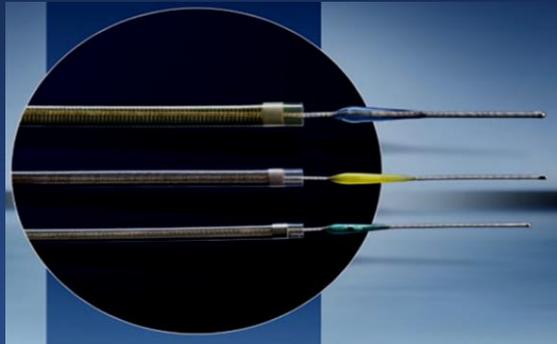
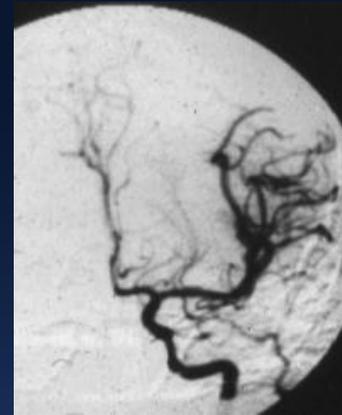
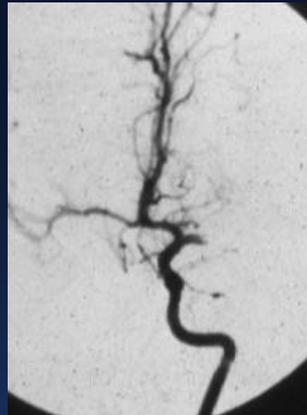
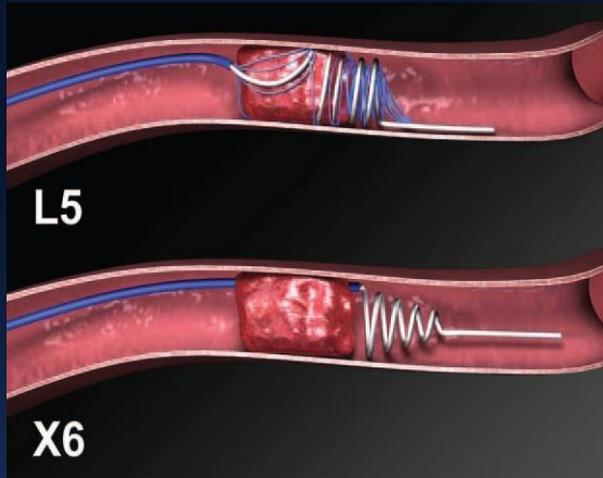


Recanalization Strategies

- FDA approved / cleared interventions:
 - IV tPA (0-3 hours) Approved 1996
 - IV tPA (3-4.5 hours) Denied request 2012
2013 AHA Recommends
 - Thrombectomy devices Cleared for clot removal

Time Window	0-3 hrs	3-4.5 hrs	3-6 hrs	8 hrs
Options	<ul style="list-style-type: none"> • IV tPA • Device 	<ul style="list-style-type: none"> • IV tPA • Device 	<ul style="list-style-type: none"> • IA Lytic • Device 	<ul style="list-style-type: none"> • Device

Intra-arterial Strategies

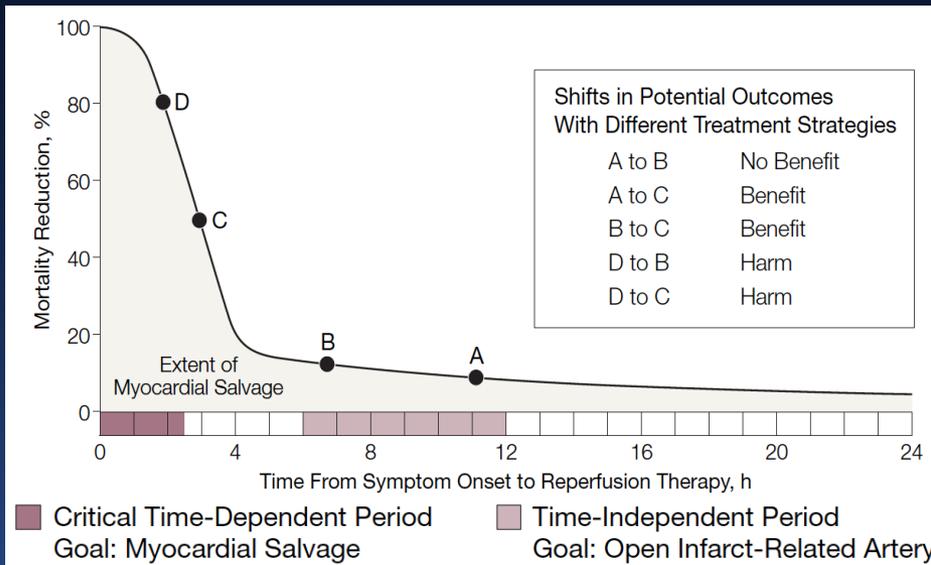




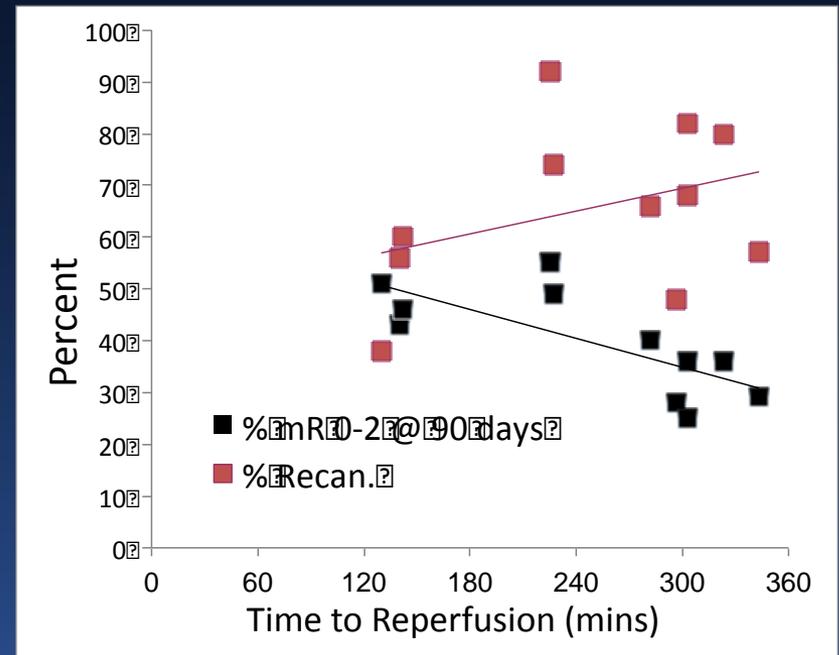
Recanalization Trials

Impact of Time

Hypothetical Benefit of Cardiac Reperfusion



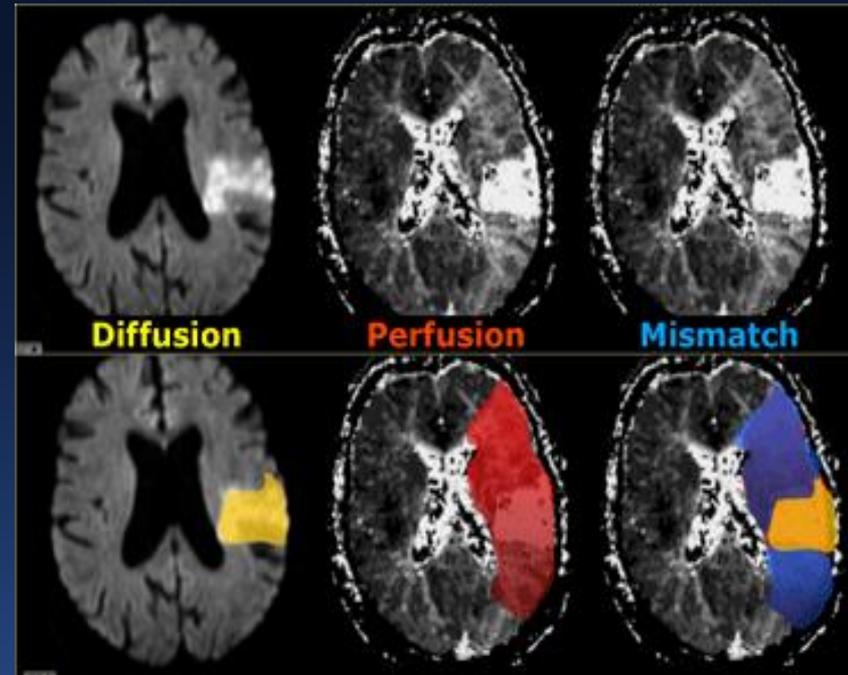
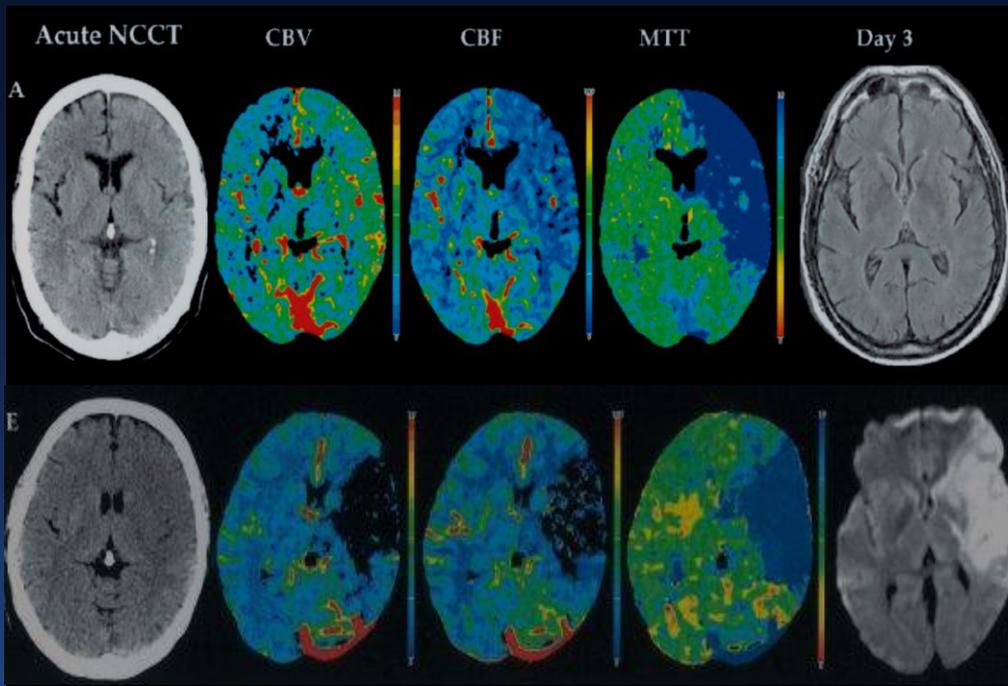
Intraarterial Reperfusion in Stroke



The Future of Stroke Treatments

- Prevention Prevention Prevention
 - Stroke Systems of Care
 - Stroke Research
 - Stroke clinical trial networks
 - New diagnostic tools
 - Thrombolytics
 - Intra-arterial approaches
 - Combination agents
 - Refining and defining windows
 - Cerebral protection
 - Surgical
 - Rehabilitation
- Neuroimaging, markers
ProUK, TNK, rPA, Ancrod
IA, specialty catheters, devices
Antiplatelets, LMWH
Clinically, imaging based
Hypothermia, neuroprotection
Hemicraniectomy, cell transplant
Constraint therapy

Penumbra Imaging



Top \uparrow CBV \uparrow MTT with penumbra \rightarrow small stroke

Bottom \downarrow CBV \uparrow MTT \rightarrow no penumbra to save \rightarrow big stroke

The Future: Full Integration of Care

Diagnosis and Treatment During Transport



Advanced Brain Imaging / Diagnostic Markers

**Prompt Recognition
911 Activation
Priority Dispatch**

EMS Triage to Most Appropriate Regional Stroke Center

Stroke Unit / NSICU



Stem cells / Nerve growth stimulants



Thrombolytic and Neuroprotective Drugs / Direct Reperfusion Strategies

Computer Assisted Therapy

**Full Recovery
Prevention Strategies**

WILL GIVE
TPA
FOR FOOD

ASA Policy Recommendations

Recommendations for the Establishment of Stroke Systems of Care

Recommendations From the American Stroke Association's Task Force on the Development of Stroke Systems

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Interactions Within Stroke Systems of Care: A Policy Statement From the American Heart Association/American Stroke Association

Randall Higashida, Mark J. Alberts, David N. Alexander, Todd J. Crocco, Bart M. Demaerschalk, Colin P. Derdeyn, Larry B. Goldstein, Edward C. Jauch, Stephan A. Mayer, Neil M. Meltzer, Eric D. Peterson, Robert H. Rosenwasser, Jeffrey L. Saver, Lee Schwamm, Debbie Summers, Lawrence Wechsler and Joseph P. Wood



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Schwamm, *Circulation* 2005;111:1078-191
Higashida, *Stroke* 2013;44



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Lecture Overview

- Review current state of acute stroke
- Review similarities and differences in cerebrovascular and cardiovascular reperfusion
- Review other acute strategies at improving functional outcomes