OPENING THE WINDOW OF TIME IN STROKE THERAPY

New Evidence for the Emergency Department

Course Chair:

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Meeting the Criteria for Intravenous Thrombolysis

Kama Guluma, MD

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Meeting the Criteria for Intravenous Thrombolysis

Objectives

1. Understand the time-critical nature of acute ischemic stroke
2. Understand factors at play in using intravenous thrombolysis safely
3. Understand how extremes of severity and age impact thrombolysis decision-making in the ED

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“Time is brain”

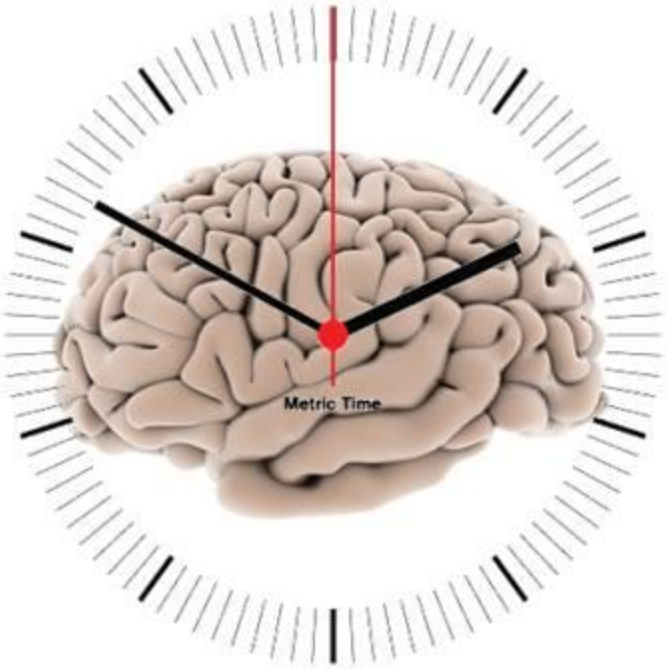

Table 5. ED-Based Care

Action	Time
Door to physician	≤10 minutes
Door to stroke team	≤15 minutes
Door to CT initiation	≤25 minutes
Door to CT interpretation	≤45 minutes
Door to drug (≥80% compliance)	≤60 minutes
Door to stroke unit admission	≤3 hours

Jauch EC, et al; AHA Stroke Council; et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870-947.

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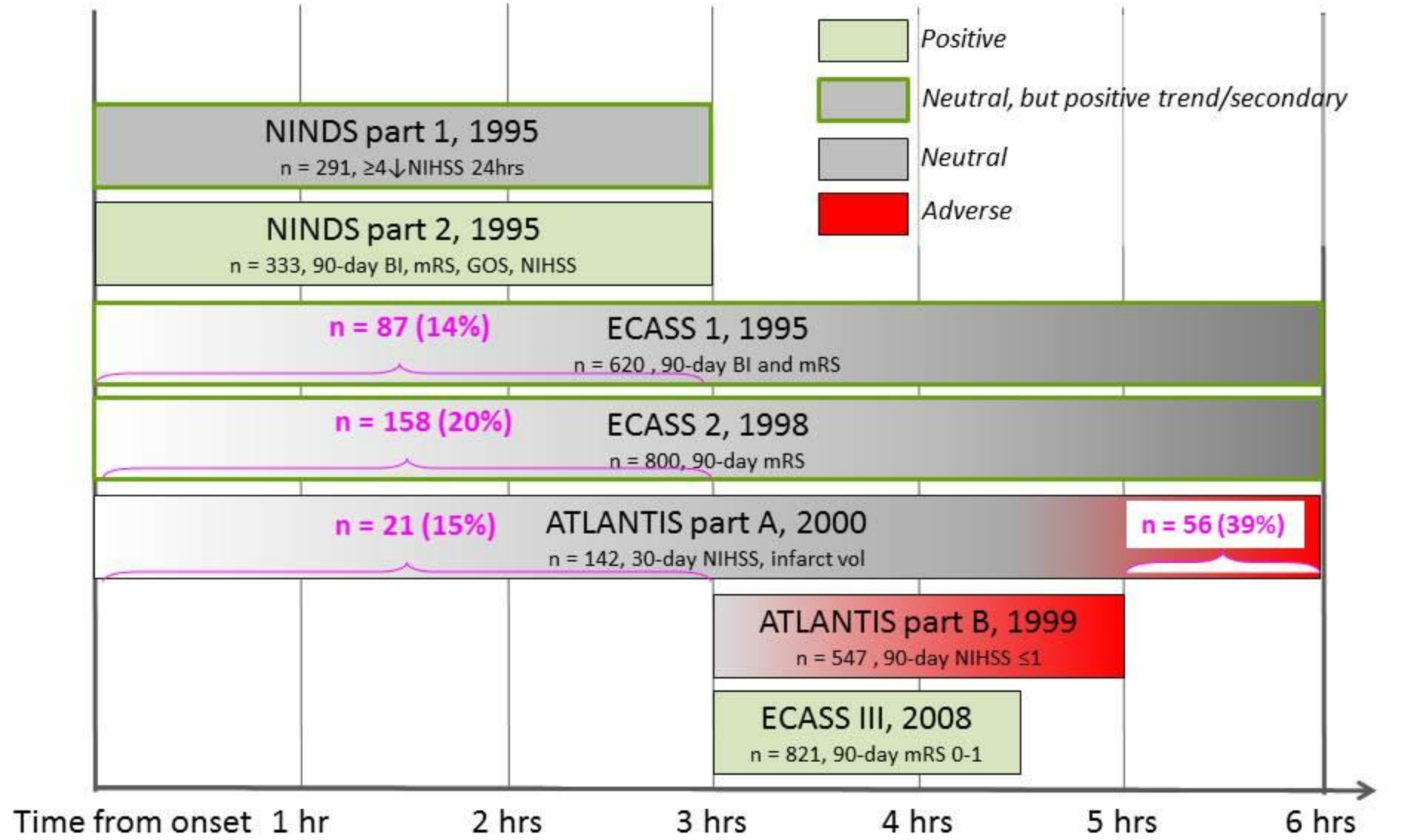
t-PA: Time-to-treatment and Efficacy



NINDS Group. *N Engl J Med*.1995; 333:1581-1588; Hacke W, et al. *JAMA*. 1995 Oct 4;274(13):1017-1025; Hacke W, et al. *Lancet*. 1998 Oct 17;352(9136):1245-1251; Clark WM, et al. *Stroke*. 2000 Apr;31(4):811-816; Clark WM, et al. *JAMA*. 1999 Dec 1;282(21):2019-2026; ECASS Investigators. *N Engl J Med*. 2008; 359:1317-1329.

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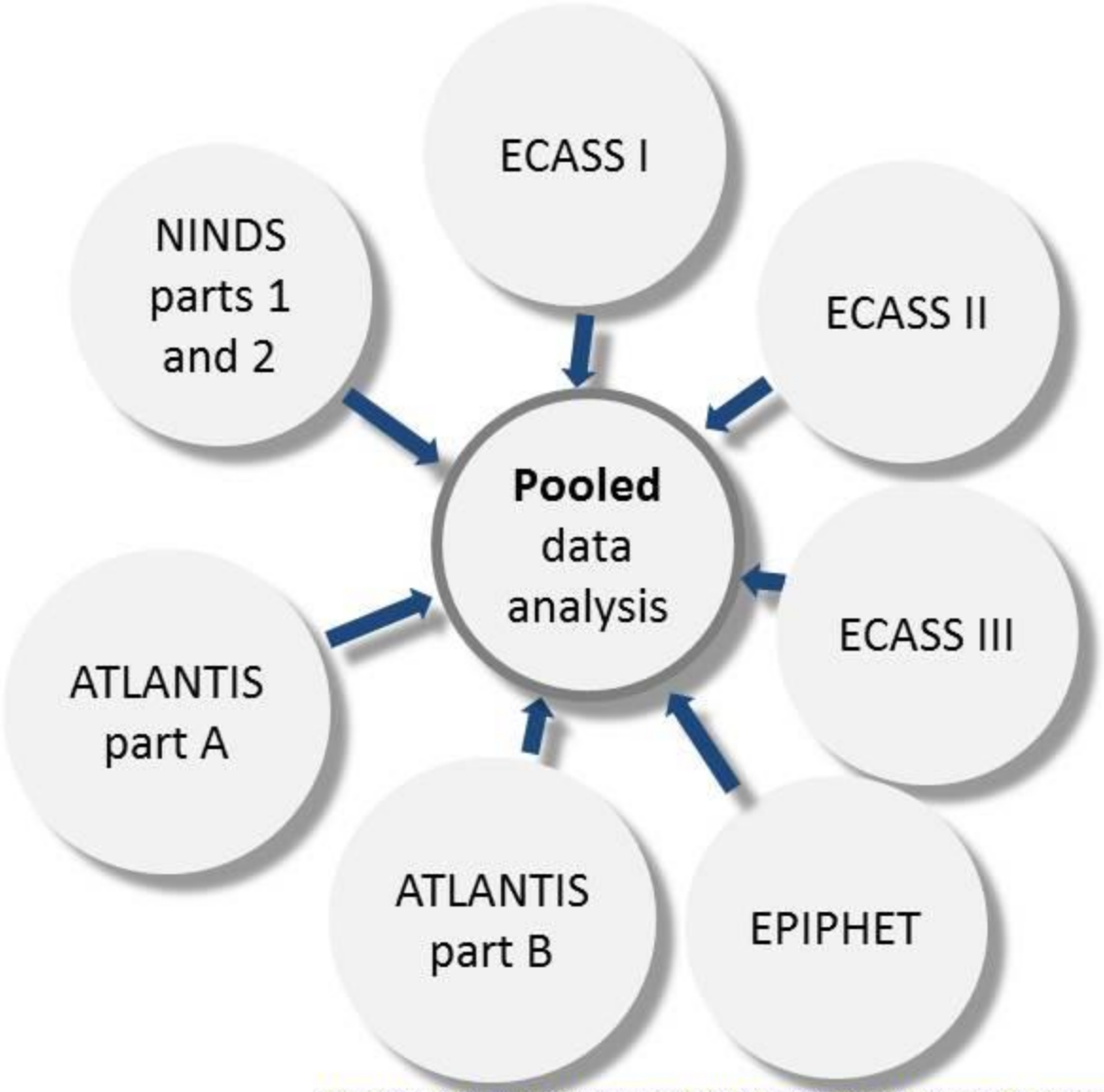
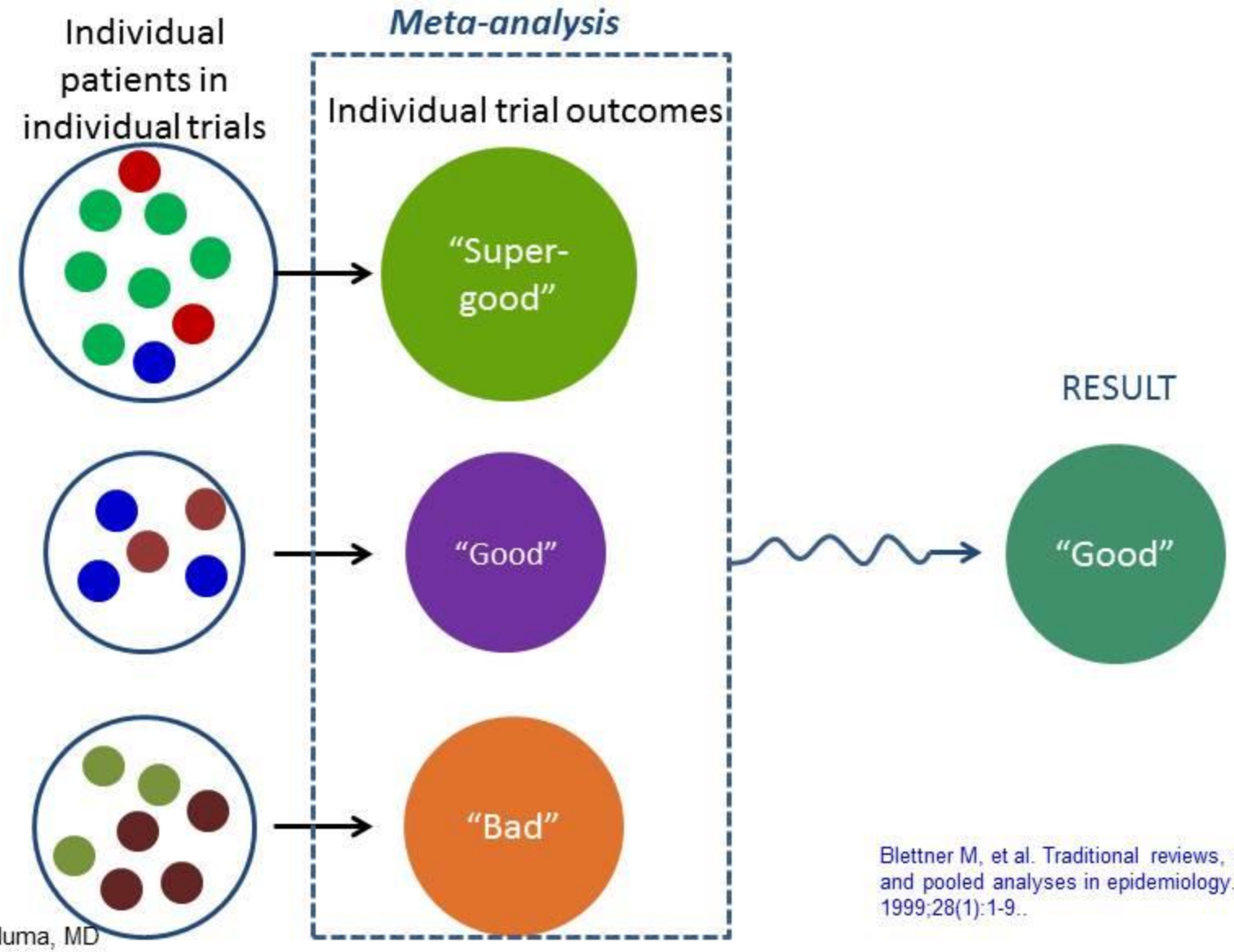
t-PA: Time-to-treatment and Efficacy



Lees KR, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375(9727):1695-703.

Meta-analysis



Blettner M, et al. Traditional reviews, meta-analyses and pooled analyses in epidemiology. Int J Epidemiol. 1999;28(1):1-9..

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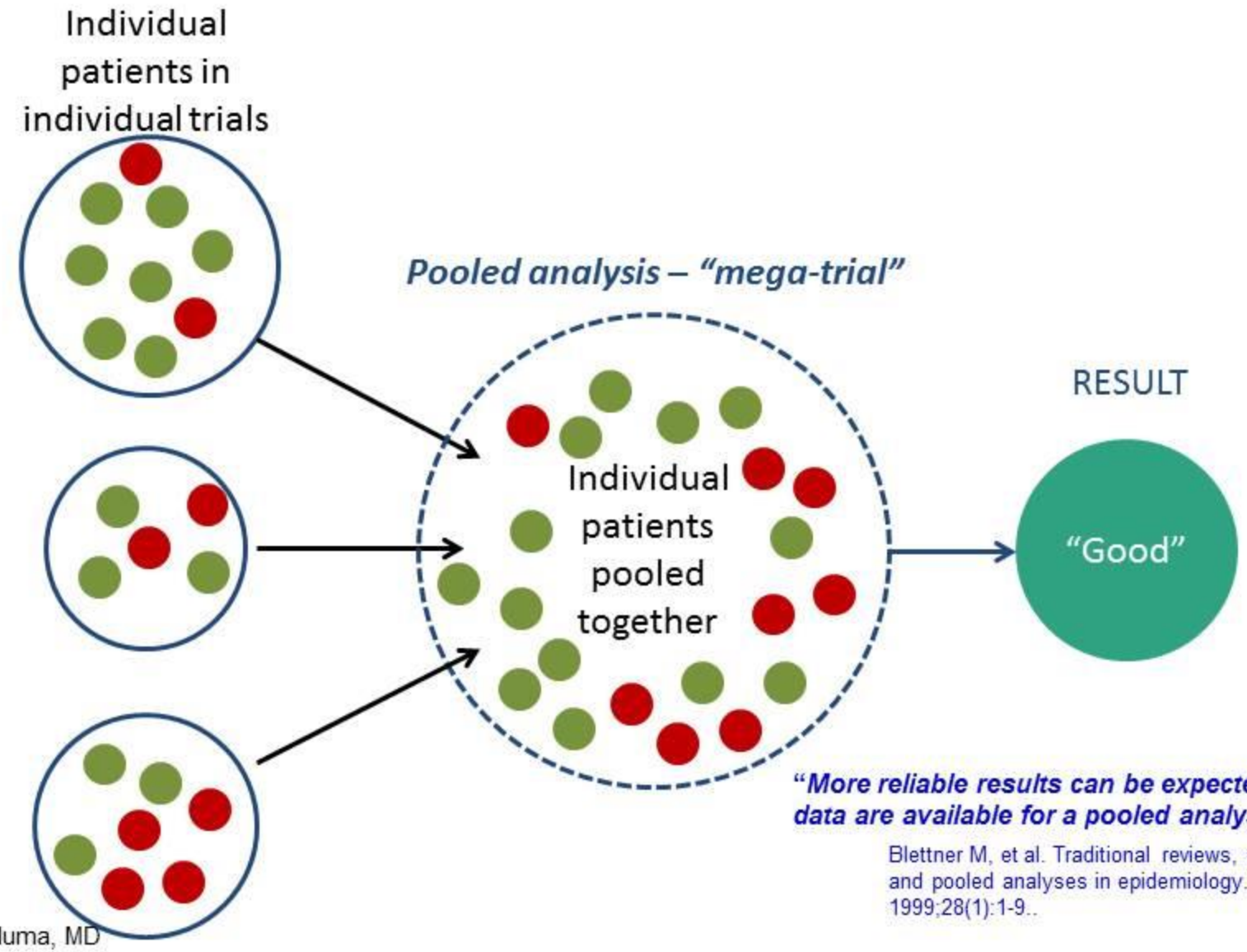
Pooled analysis



"More reliable results can be expected if individual data are available for a pooled analysis…"

Blettner M, et al. Traditional reviews, meta-analyses and pooled analyses in epidemiology. Int J Epidemiol. 1999;28(1):1-9..

t-PA: Time-to-treatment and Efficacy

- Lees pooled analysis (N = 3,670)
  - Increased t-PA efficacy with earlier administration
    - No further efficacy demonstrated after 4.5 hours
  - Mortality benefit seen with t-PA administration
    - This benefit decreased the later t-PA was administered
    - Risk of administration after 4.5 hours may outweigh benefit

Lees KR, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375(9727):1695-703.

t-PA: Time-to-treatment and Efficacy

- At anytime t-PA is administered, there is a risk of symptomatic hemorrhage

Lees KR, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375(9727):1695-703.

Using t-PA safely; Exclusion Criteria

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Tomandl BF, et al. Comprehensive imaging of ischemic stroke with multisection CT. Radiographics. 2003;23(3):565-92.

Using t-PA safely

Exclusion criteria

t-PA exclusion criteria

"Leaky brain or leak*ing* body"

- Significant **head trauma** or prior **stroke** in previous 3 months
- Symptoms suggest **subarachnoid** hemorrhage
- Recent **intracranial** or intraspinal **surgery**
- **Active internal bleeding**
- **Arterial puncture** at noncompressible site in previous 7 days

"Bad brain"

- Intracranial **neoplasm**, **arteriovenous** malformation, or **aneurysm**
- History of **previous intracranial hemorrhage**
- CT demonstrates multilobar infarction (**hypodensity >1/3 cerebral hemisphere**)

Jauch EC, et al; AHA Stroke Council; et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870-947.

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Using t-PA safely

Exclusion criteria

t-PA exclusion criteria

Bleeding diathesis

- **Platelet count <100 000/mm³**
- **Heparin** within 48 hours, with **elevated aPTT**
- Current use of **anticoagulant** with **INR >1.7 or PT >15 seconds**
- **Direct thrombin inhibitors or direct factor Xa inhibitors** with "elevated sensitive laboratory tests"

Miscellaneous

- Blood **glucose** concentration **<50** mg/dL (2.7 mmol/L)
- **Elevated blood pressure** (systolic >185 mm Hg or diastolic >110 mm Hg)

Jauch EC, et al; AHA Stroke Council; et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870-947.

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Using t-PA safely

Exclusion criteria

RELATIVE t-PA exclusion criteria

Relative exclusions

- **Minor or rapidly improving** symptoms
- **Pregnancy**
- **Seizure** at onset with residual neurological impairments
- **Major surgery or serious trauma** within previous 14 days
- **Recent GI or GU hemorrhage** (within previous 21 days)
- **Recent AMI** (within 3 months)

For treatment at 3 – 4.5 hours

- Aged **>80 years**
- Severe stroke (**NIHSS>25**)
- Taking an **oral anticoagulant** regardless of INR
- History of **both diabetes and prior ischemic stroke**

Jauch EC, et al; AHA Stroke Council; et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870-947.

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Using t-PA safely; treatment decisions

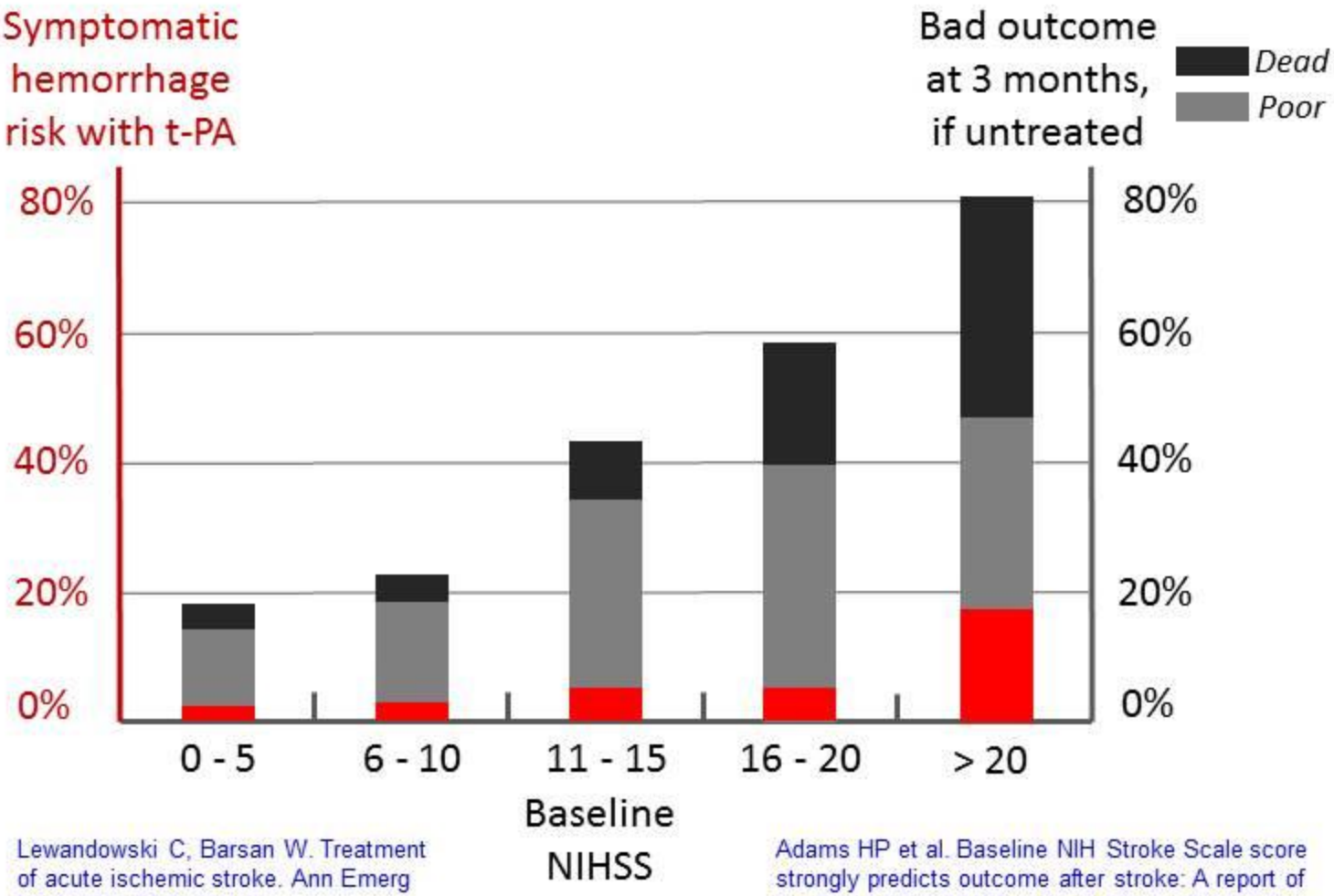
Is the patient too severe?

Is the patient too mild?

Is the patient too old?

Using t-PA safely

Treatment decisions



Lewandowski C, Barsan W. Treatment of acute ischemic stroke. Ann Emerg Med. 2001;37(2):202-16.

Adams HP et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology. 1999;53(1):126-31.

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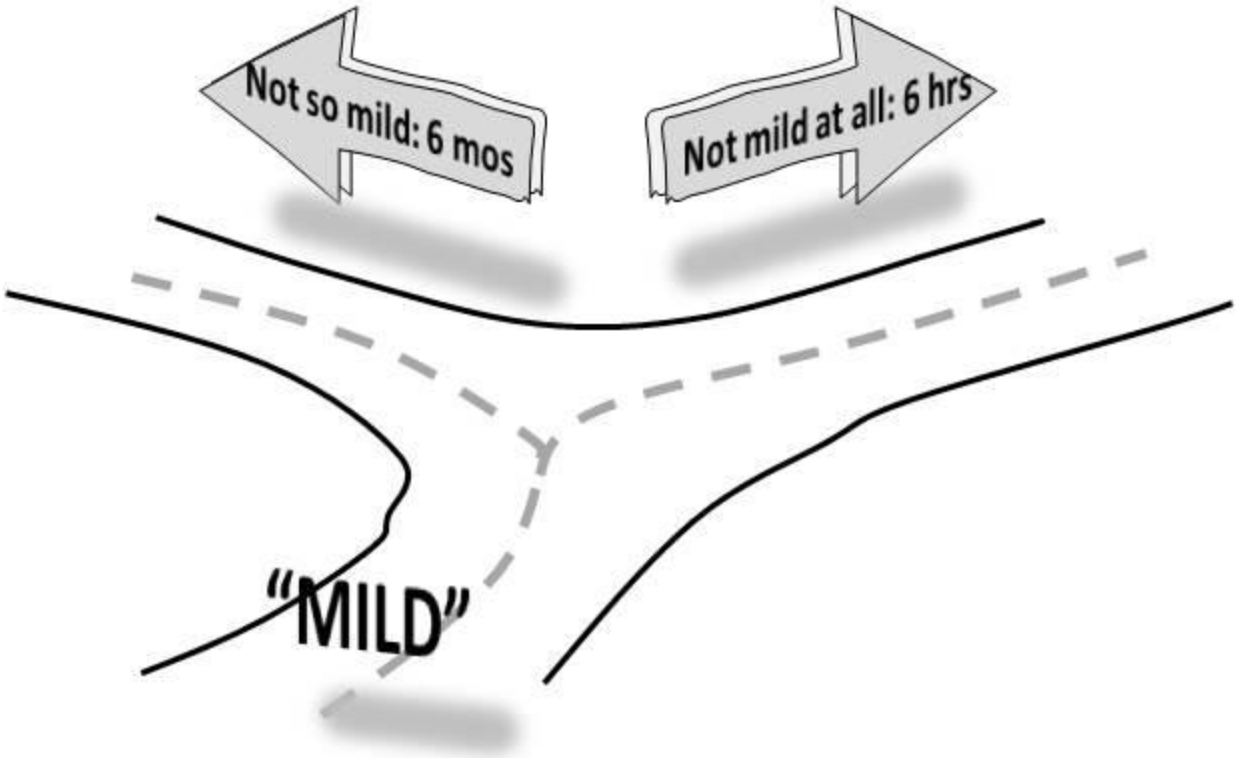
Using t-PA safely

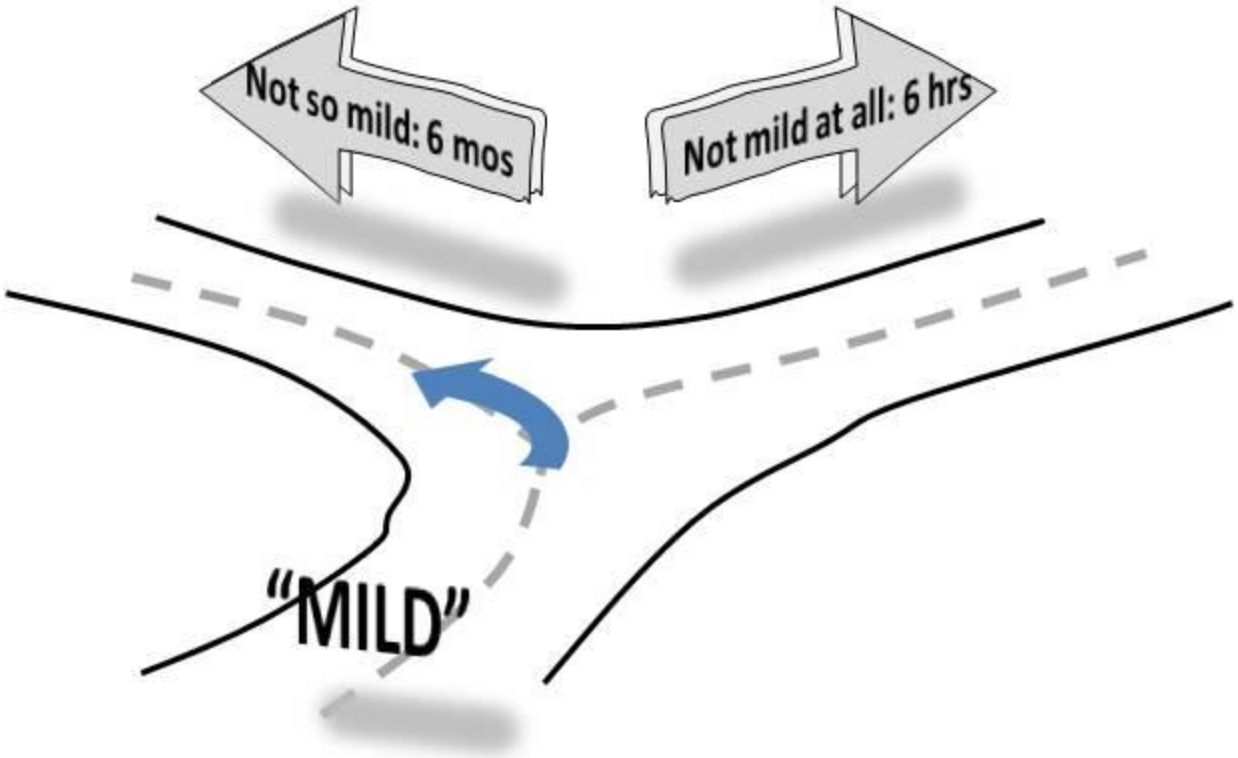
Treatment decisions



Is the patient too mild?

Using t-PA safely

Treatment decisions



Is the patient too mild?

Consideration:
the "low NIHSS score" stroke with a devastating effect on livelihood

Using t-PA safely

Treatment decisions

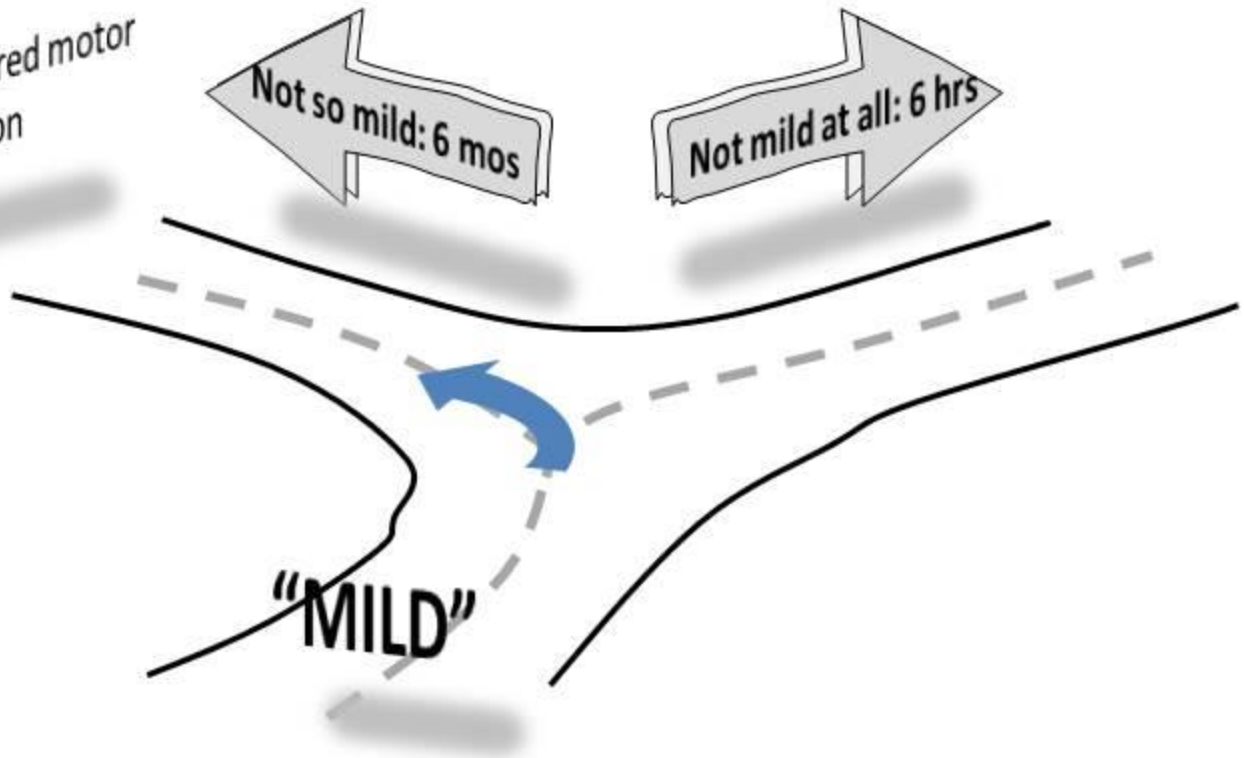
Carlsson GE, et al Consequences of mild stroke in persons< 75 years–a 1-year follow-up. Cerebrovasc Dis 2003;16:383-388

Clarke PJ, Handicap in stroke survivors. Disabil Rehabil. 1999;21:116-123.

Edwards DF, et al. The impact of mild stroke on meaningful activity and life satisfaction. J Stroke Cerebrovasc Dis. 2006;15(4):151-7.

Stewart JC, Cramer SC. Patient-reported measures provide unique insights into motor function after stroke. Stroke. 2013;44(4):1111-6.

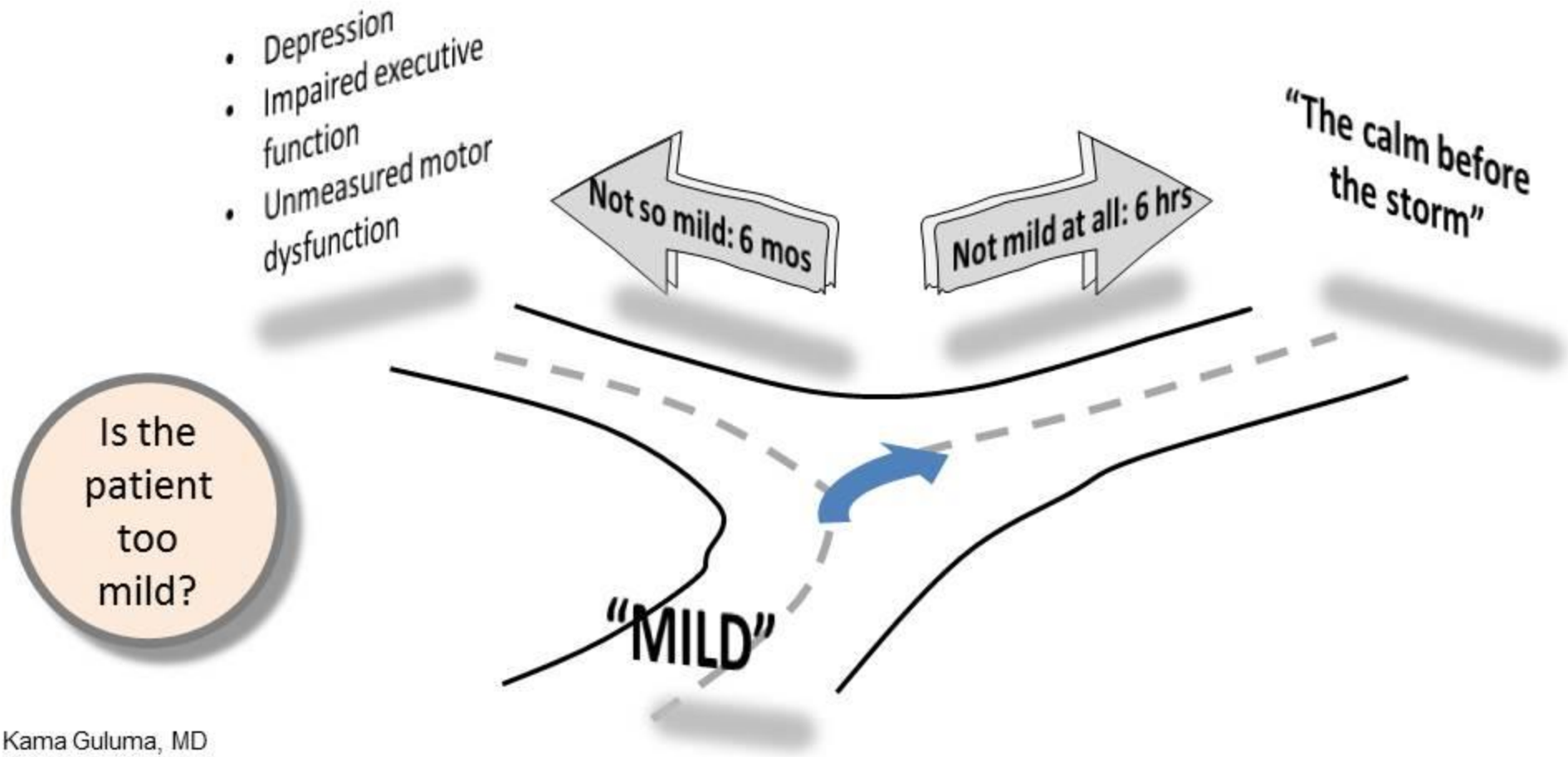
- Depression
- Impaired executive function
- Unmeasured motor dysfunction



Is the patient too mild?

Using t-PA safely

Treatment decisions

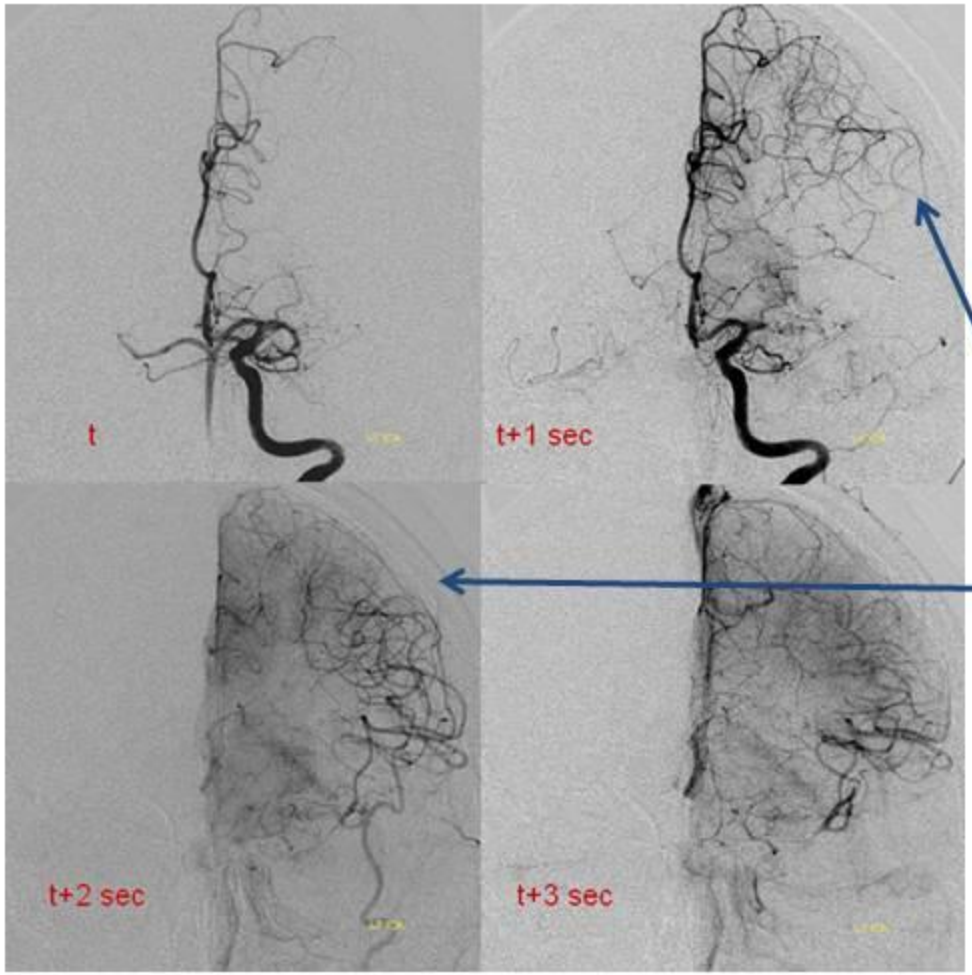


Using t-PA safely

Treatment decisions

Is the patient too mild?

Not mild at all: 6 hrs



"The calm before the storm"

ACA-to-MCA collaterals in an MCA stroke

http://neuroangio.org/neuroangio-topics/intracranial-collateral-pathways/

Using t-PA safely

Treatment decisions

Is the patient too mild?

Rapid improvement

+

Large-vessel occlusion or stenosis on imaging (especialy if present while deficit is mild)

OR

Symptoms consistent with a large vessel occlusion/cortical stroke

↓

...is associated with subsequent deterioration

"The calm before the storm"

Alexandrov AV et al. Deterioration following spontaneous improvement : sonographic findings in patients with acutely resolving symptoms of cerebral ischemia. Stroke. 2000;31(4):915-9.

Johnston SC, et al. Early recovery after cerebral ischemia risk of subsequent neurological deterioration. Ann Neurol. 2003;54:439–444.

Smith EE, et al. Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. Stroke. 2005; 36: 2497–2499.

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Using t-PA safely

Treatment decisions

Use in Acute Ischemic Stroke

In addition to the previously listed conditions, the risks of alteplase therapy to treat acute ischemic stroke may be increased in the following conditions and should be weighed against the anticipated benefits:

- Patients with severe neurological deficit (e.g., NIHSS > 22) at presentation. There is an increased risk of intracranial hemorrhage in these patients.
- Patients with major early infarct signs on a computerized cranial tomography (CT) scan (e.g., substantial edema, mass effect, or midline shift).

Using t-PA safely

Treatment decisions

NIHSS

Imaging

Using t-PA safely

Treatment decisions

Is the patient too severe?

Lewandowski C, Barsan W. Treatment of acute ischemic stroke. Ann Emerg Med. 2001;37(2):202-16.

NIHSS

Risk of symptomatic ICH by baseline NIHSS in NINDS

NIHSS	ICH (%)
1 – 5	2%
6 – 10	3%
11 – 15	5%
16 – 20	5%
> 20	17%

Imaging

Using t-PA safely

Treatment decisions

Is the patient too severe?

NIHSS

Risk of symptomatic ICH by baseline NIHSS in NINDS

NIHSS	ICH (%)
1 – 5	2%
6 – 10	3%
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16 – 20	5%
> 20	17%

Imaging

Using t-PA safely

Treatment decisions

Is the patient too severe?

Szoeke CE, et al. Med J Aust. 2003;178:324-328.

Wahlgren N, et al. Lancet. 2007;369:275-282.

Ahmed N, et al. Lancet Neurol. 2010;9:866-874.

Norris JW, et al. Can J Neurol Sci. 1998;25:257-259.

Adams HP Jr, et al. Stroke. 2007; 38:1655-1711.

Albers GW, et al. Chest. 2004;126:483S-512S.

NIHSS

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NIHSS	ICH (%)
1 – 5	2%
6 – 10	3%
11 – 15	5%
16 – 20	5%
> 20	17%

> 1/3 the territory of the MCA

Imaging

Using t-PA safely

Treatment decisions

Is the patient too severe?

NIHSS

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1 – 5	2%
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Imaging

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Using t-PA safely

Treatment decisions

NIHSS

Risk of symptomatic ICH by baseline NIHSS in NINDS

NIHSS	ICH (%)
1 – 5	2%
6 – 10	3%
11 – 15	5%
16 – 20	5%
> 20	17%

Imaging

> 1/3 the territory of the MCA?

Is the patient too severe?

Time since onset

00:00.0

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Using t-PA safely

Treatment decisions

Using t-PA safely

Treatment decisions

Is the patient too old?

YOUNG

OLD fare worse with stroke

Pohjasvaara T, et al. Comparison of stroke features and disability in daily life in patients with ischemic stroke aged 55 to 70 and 71 to 85 years. Stroke. 1997;28(4):729-35.

Sharma JC, et al. Strokes in the elderly - higher acute and 3-month mortality - an explanation. Cerebrovasc Dis. 1999;9(1):2-9.

Kammersgaard LP, et al; Copenhagen Stroke Study. Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. Age Ageing. 2004;33(2):149-54.

Soares I, et al. Outcome of first-ever acute ischemic stroke in the elderly. Arch Gerontol Geriatr. 2011;53(2):e81-7.

Using t-PA safely

Treatment decisions

Is the patient too old?

YOUNG

OLD fare worse with stroke

Less aggressive workups & treatment

Di Carlo A, et al. Stroke in the very old : clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. Stroke. 1999;30(11):2313-9.

Using t-PA safely

Treatment decisions

Is the patient too old?

YOUNG

YOUNG do better with t-PA

OLD fare worse with stroke

OLD still benefit too

Heuschmann PU, et al. Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. JAMA. 2004;292(15):1831-8.

Mouradian MS, et al. Intravenous rt-PA for acute stroke: comparing its effectiveness in younger and older patients. J Neurol Neurosurg Psychiatry. 2005;76(9):1234-7.

Bhatnagar P, et al. Intravenous thrombolysis in acute ischaemic stroke: a systematic review and meta-analysis to aid decision making in patients over 80 years of age. J Neurol Neurosurg Psychiatry. 2011;82(7):712-7.

Di Carlo A, et al. Stroke in the very old : clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. Stroke. 1999;30(11):2313-9.

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Using t-PA safely

Treatment decisions

Is the patient too old?

YOUNG

OLD fare worse with stroke

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OLD still benefit too

Leevi N, et al. Acute stroke management in the elderly. Cerebrovasc Dis. 2007;23(4):304-8.

Mishra NK, et al, VISTA collaborators; SITS collaborators. Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. BMJ. 2010;341:c6046.

de Weerd L, et al. Quality of life of elderly ischaemic stroke patients one year after thrombolytic therapy. A comparison between patients with and without thrombolytic therapy. BMC Neurol. 2012;12:61.

IST-3 collaborative group. Lancet. 2012;379(9834):2352-63.

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Using t-PA safely

Treatment decisions

Is the patient too old?

YOUNG

YOUNG do better with t-PA

OLD fare worse with stroke

OLD still benefit too

Age >80 = increased ICH risk with t-PA

Larrue V, et al. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). Stroke. 2001;32(2):438-41.

Hacke W, et al; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363(9411):768-74.

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Using t-PA safely

Treatment decisions

Berrouschot J, et al. Outcome and severe hemorrhagic complications of intravenous thrombolysis with tissue plasminogen activator in very old (> or =80 years) stroke patients. Stroke. 2005;36(11):2421-5..

Engelter ST, et al. Intravenous thrombolysis in stroke patients of > or = 80 versus < 80 years of age--a systematic review across cohort studies. Age Ageing. 2006;35(6):572-80.

Lansberg MG, et al. Symptomatic intracerebral hemorrhage following thrombolytic therapy fo ischemic stroke: a review of the risk factors. Cerebrovasc Dis. 2007;24(1):1-10

Pundik S, et al. Older age does not increase risk of hemorrhagic complications after intr intra-art s for acute stroke. J Stroke Cerebrovasc Dis. 2008;17(5):266-72

Bh s thrombolysis in acute i stroke: a systematic revie an g in patients over 8 leurol Neur ag Psychi 20

Sy eplase Stol SES) Investigators. Thrombolysis i rs with acute isc teplase for Stroke Effectiveness y. Psychiatry. 2006;7

al. Intravenous tissu plasminogen a chemic stroke in patients der : the t-PAstroke su y experience. ;31(2):370-5.

A Study Group]. Generalized cacy of t-PA for acute stroke. Subgroup analy A Stroke Trial. Stroke. 1997;28(1 119

Is the patient too old?

YOUNG

YOUNG do better with t-PA

OLD fare worse with stroke

OLD still benefit too

Age >80 ≠ increased ICH risk with t-PA

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Using t-PA safely

Treatment decisions

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Engelter ST, et al. Intravenous thrombolysis in stroke patients of > or = 80 versus < 80 years of age--a systematic review across cohort studies. Age Ageing. 2006;35(6):572-80.

Lansberg MG, et al. Symptomatic intracerebral hemorrhage following thrombolytic therapy for acute ischemic stroke: a review of the risk factors. Cerebrovasc Dis. 2007;24(1):1-10

Pundik S, et al. Older age does not increase risk of hemorrhagic complications after intravenous and/or intra-art… …s for acute stroke. J Stroke Cerebrovasc Dis. 2008;17(5):266-72.

Bha… …s thrombolysis in acute ischaemic stroke: a systematic review and meta-an… …g in patients over 80 years of age. J Neurol Neurosurg Psychiatry. 20…

Sy… …teplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis in pa… …ars with acute ischaemic stroke: Canadian Alteplase for Stroke Effectiveness Study. … …g Psychiatry. 2006;77(7):826-9.

Tanne D, et al. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older : the t-PAstroke survey experience. Stroke. 2000;31(2):370-5.

[NINDS t-PA Study Group]. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA Stroke Trial. Stroke. 1997;28(11):2119-25.

Is the patient too old?

THE CATCH

Most data obtained outside a RCT

Selection bias?

Using t-PA safely

Treatment decisions

Subgroup	Events/Number of patients		Adjusted Odds Ratio (99% CI)	Adjusted p value
	rt-PA	Control		
Age (years)				0.029
≤80	331/698 (47.4%)	346/719 (48.1%)	0.92 (0.67-1.26)	
>80	223/817 (27.3%)	188/799 (23.5%)	1.35 (0.97-1.88)	
NIHSS Score				0.003
0-5	221/304 (72.7%)	232/308 (75.3%)	0.85 (0.52-1.38)	
6-14	276/728 (37.0%)	268/724 (37.0%)	1.08 (0.81-1.45)	
15-24	50/402 (12.4%)	33/421 (7.8%)	1.73 (0.93-3.20)	
≥25	7/81 (8.6%)	1/65 (1.5%)	7.43 (0.43-129.00)	

IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379(9834):2352-63

Summary

TIME *REALLY* IS BRAIN:

- Minute-by-minute reduction of good outcome with t-PA, until it's gone by 4.5 hours from onset

Is the patient too mild?

WATCH OUT FOR:

- Small strokes with big consequences
- Rapid improvement of cortical/large artery strokes

Is the patient too severe?

- < 3 hours: Careful with NIHSS > 22
- 3 – 4.5 hrs: Avoid NIHSS > 25
- Anytime: Avoid hypodensity >1/3 hemisphere on CT

Is the patient too old?

- < 3 hours: "Never too old", but careful with age > 80
- 3 – 4.5 hrs: Be **very** careful with age > 80

How Policy Affects Practice in Stroke Therapy

Andy S. Jagoda, MD

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Department of Emergency Medicine
Mount Sinai School of Medicine
New York, NY

Key Questions

- Are there guidelines that assist in clinical decision making? How good are they?
  - ACEP/AAN Clinical Practice Guidelines
  - AHA/ASA Guidelines for the Early Management of Adults with Ischemic Stroke
- Have policy and guidelines changed outcomes?

Evidence-based Guidelines

- Define the clinical question
  - Focused question better than global question
  - Outcome measure must be determined
- Grade the strength of evidence
- Incorporate practice patterns, available expertise, resources and risk:benefit ratios

Two Separate Questions

- How strong is the evidence from one study?
  - Critical appraisal
- How strong is the combined evidence from multiple studies?
  - Synthesis
  - Consistency in magnitude, direction
- Greater risk, cost, implausibility require greater evidence

Evidence-based Guidelines: Limitations

- Different groups can read the same evidence and come up with different recommendations
- Outcome measure can be major factor
  - MTBI
  - t-PA in stroke
  - Steroids in spinal trauma

Description of the Process

- Different societies use different classification schemes which may impact applications of the recommendation
- ASA / AHA

Description of the ACEP Process

- Strength of evidence (Class of evidence)
  - I: Randomized, double-blind interventional studies for therapeutic effectiveness; prospective cohort for diagnostic testing or prognosis
  - II: Retrospective cohorts, case control studies, cross-sectional studies
  - III: Observational reports; consensus reports
- Strength of evidence can be downgraded based on methodological flaws

American College of Emergency Physicians: Clinical Policy Development. www.acep.org/clincialpolicies/?pg=1. Accessed 30 Sept 2014.

Description of the ACEP Process

- Strength of recommendations:
  - A / Standard: Reflects a high degree of certainty based on Class I studies
  - B / Guideline: Moderate clinical certainty based on Class II studies
  - C / Option: Inconclusive certainty based on Class III evidence

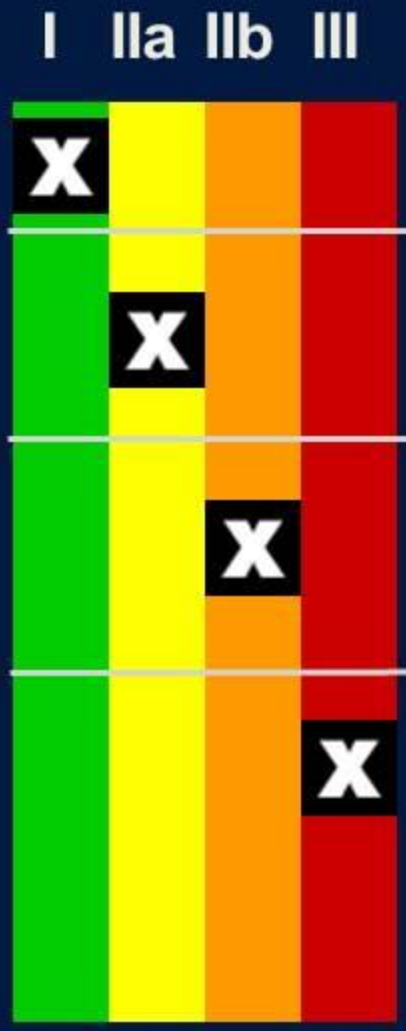
American College of Emergency Physicians: Clinical Policy Development. www.acep.org/clincialpolicies/?pg=1. Accessed 30 Sept 2014.

Description of the ASA Process: Levels of Evidence

- Level A
  - Data from many large, randomized trials
- Level B
  - Data from fewer, smaller randomized trials, careful analyses of nonrandomized studies, observational registries
- Level C
  - Expert consensus

Jauch EC, et al. *Stroke*. 2013;44(3):870-947.

Description of the ASA Process: Classes of Recommendations



Intervention is useful and effective

Evidence conflicts/opinions differ but leans toward efficacy

Evidence conflicts/opinions differ; neutral statement

Intervention is not useful/effective and may be harmful

Jauch EC, et al. *Stroke*. 2013;44(3):870-947.

Why Don't Physicians Follow Clinical Practice Guidelines?

- Review of 76 articles dealing with adherence
- Barriers to physician adherence identified:
  - Lack of familiarity
  - Lack of agreement
  - Lack of access to intervention or resource
  - Lack of confidence that an intervention will change the outcome
  - Patient related barriers

Cabana MD, et al. *JAMA*. 1999;282(15):1458-1465.

2006 Recommendations for Use of Thrombolytic Agents

- American Academy of Emergency Medicine
  - "Insufficient evidence"
- Society for Academic Emergency Medicine
  - "Insufficient evidence"
- National Heart, Lung and Blood Institute
  - 0 - 3 hrs (Grade IA)
  - 3+ hrs not recommended
- American Heart Association
  - 0 - 3 hrs t-PA is recommended (Grade IA)
- American College of Emergency Physicians
  - "Insufficient evidence at this time to endorse the use of intravenous t-PA…when systems are not in place"
  - t-PA may be an efficacious therapy…if used according to NINDS criteria

Adams HP, et al. *Circulation*. 2007;115(20):e478-534.
Goyle GD, et al. Position Statement on the Use of Intravenous Thrombolytic Therapy in the Treatment of Stroke. 2002. www.aaem.org.

2014 Recommendations for Use of Thrombolytic Agents

- American Academy of Emergency Medicine
  - 0 - 3 confirmed benefit
  - 3 - 4.5 suggested benefit
- Society for Academic Emergency Medicine
  - Rescinded statement
- National Heart, Lung and Blood Institute/American Heart Association
  - 0 - 3 hrs (Grade IA)
  - 3 - 4.5 hrs (Grade 1B)
- American College of Emergency Physicians
  - 0 - 3 hrs t-PA should be offered (Level A)
  - 3 - 4.5 hrs t-PA should be considered (Level B)

ACEP. Clinical Policy: Use of intravenous t-PA for the management of acute ischemic stroke in the ED. Ann Emerg Med 2013; 61z; 225-243.
AAEM. Clinical practice statement: t-PA and stroke. 4.12.10

Thrombolysis for Acute Ischemic Stroke

- 27 trials; 10,187 participants
- "People given clot dissolving drugs were more likely to have recovered from their stroke and to be independent, especially if they had been treated within the first 3 hours"
- "Older people benefited as much as younger people"
- "The treatment is very effective if started within 3 hours of stroke and definitely improves outcome if given up to 4.5 hours after stroke"

Wardlaw JM, et al. *Cochrane Database Syst Rev.* 2014;7:CD000213.

Do the BAC's Criteria for Stroke Centers Improve Care for Ischemic Stroke?

- Questionnaire regarding the BAC 11 elements sent to 34 academic medical centers
  - 85% had a recognized stroke team
  - 85% had a stroke unit
  - 16,853 acute ischemic stroke cases between 1999 - 2001
    - 2.4% received t-PA
- Written protocols were associated with increased t-PA use

Douglas VC, et al. *Neurology.* 2005:64(3):422-427.

Houston Paramedic and Emergency Stroke Treatment and Outcome Study

- Educational interventional study: 1999 - 2001
  - Phase 1 – Baseline data collection
  - Phase 2 – Educational program to paramedics, public messaging, community screening
- Cases per month increased from 74 to 89
- Paramedic diagnostic accuracy increased from 61% to 79%
- Patients arriving within 120 minutes of symptom onset increased from 58% to 62%
- Use of t-PA increased with a range from 6.8% to 17.2%
  - 3.7% hemorrhage rate

Wojner-Alexandrov AW, et al. *Stroke*. 2005;36(7):1512-1518.

Temporal Trends In Patient Characteristics and Treatment Among Acute Ischemic Stroke Patients at GWTG Stroke Hospitals

- Analysis of 1,093,895 acute stroke patients from the GWTG registry from 2003 to 2011
- 50,798 treated with t-PA
- Door-to-image time decreased from a median of 24 to 20 minutes
- Door-to-needle time decreased from a median of 81 min to 72 min
- t-PA use increased from 4% to 7% in all AIS patients
  - 42% to 77% eligible patients

Schwamm LH, et al. *Circ Cardiovasc Qual Outcomes*. 2013;6(5):543-549.

Key Points

- Alteplase is an FDA approved treatment for acute ischemic stroke and its use in the appropriate setting is a recommendation by ACEP, AAEM, AAN, ASA/AHA, ESO, NICE
- A decision not to use alteplase in the appropriate setting is acceptable but clinical decision-making must be well supported in the medical record

IV t-PA or Endovascular Procedures – Assessing the Evidence

PHILIP B. GORELICK, MD MPH FACP

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Michigan State University College of Human Medicine
Medical Director, Mercy Health Hauenstein Neurosciences
Grand Rapids, MI

Learning Objectives

The learner will be able to discuss the following new evidential sources in relation to acute ischemic stroke treatment:

1. Intravenous tissue plasminogen activator (IV t-PA)
2. Endovascular clinical trials
3. Future directions

Background Information

Time is Brain – Quantified

Estimated Loss of Key Nerve Tissue in a Typical Large Artery Hemisphere AIS

Parameter	Neurons Lost	Synapses Lost
Per Stroke	1.2 billion	8.3 trillion
Per Hour	120 million	830 billion
Per Minute	1.9 million	14 billion
Per Second	32,000	230 million

AIS= Acute Ischemic Stroke

Saver JL. *Stroke*. 2006;37(1):263-266.

Onset to Treatment Time with IV t-PA Need for Speed in Acute Ischemic Stroke

Setting

- AHA/ASA Get With The Guidelines: Stroke program registry of 58,353 t-PA treated patients

Results

- Faster onset to treatment time in 15 minute increments led to:
  1. Reduced in-hospital mortality (OR=0.96; 95% CI: 0.95, 0.98*)
  2. Symptomatic intracranial bleeding (OR=0.96; 95% CI: 0.95, 0.98*)
  3. Increase of independent ambulation at discharge (OR=1.04; 95% CI: 1.03, 1.05*)
  4. Discharge to home (OR=1.03; 95% CI: 1.02, 1.04*)

Conclusion: Rapidity or treatment significantly influences outcomes with IV t-PA in AIS

*$P<.001$

Saver JL, et al. *JAMA*. 2013;309(23):2480-2488.

The Latest Evidence Supporting Use of IV t-PA

Effect of Treatment Delay, Age, and Stroke Severity on the Effects of IV Thrombolysis with Alteplase for Acute Ischemic Stroke: A Meta-analysis of Individual Patient Data from Randomized Trials*

*NINDS A&B, ECASS I-III, ATLANTIS A&B, EPITHET, IST-3

Emberson J, et al. for the Stroke Thrombolysis Trialists' Collaboration Group.
Lancet. 2014; published online August 6th, DOI: 10.1016/S0140-6736(14)60584-5.

Effect of Alteplase for Good Outcome (mRS 0-1) by Treatment Delay, Age, and Stroke Severity-1

	Alteplase (n=3391)	Control (n=3365)	Odds Ratio (95% CI)
Treatment Delay			
0 - 3.0 hrs	32.9%	23.1%	1.75 (1.35, 2.27)*
>3.0 ≤4.5 hrs	35.3%	30.1%	1.26 (1.05, 1.51)
>4.5 hrs	32.6%	30.6%	1.15 (.95, 1.40)
Age (years)			
≤80	39.4%	33.9%	1.25 (1.10, 1.42)
>80	17.6%	13.2%	1.56 (1.17, 2.08)
Baseline NIHSS			
0 - 4	68.7%	58.9%	1.48 (1.07, 2.06)
5 - 10	47.7%	43.0%	1.22 (1.04, 1.44)
11 - 15	24.0%	21.7%	1.24 (.98, 1.58)
16 - 21	11.6%	8.2%	1.50 (1.03, 2.17)
≥22	7.1%	2.6%	3.25 (1.42, 7.47)

Emberson J, et al. for the Stroke Thrombolysis Trialists' Collaboration Group. *Lancet*. 2014; published online August 6th, DOI: 10.1016/S0140-6736(14)60584-5. CI= confidence interval; mRS= modified Rankin score. *>1 favors alteplase; NIHSSS= National Institutes of Health Stroke Scale Score

Effect of Alteplase for Good Outcome (mRS 0-1) by Treatment Delay, Age, and Stroke Severity-3

Bottom line

- Irrespective of age, stroke severity, and despite an increased risk of fatal ICH early after treatment, alteplase significantly improves odds of a good outcome after stroke within 4.5 hours

Emberson J, et al. for the Stroke Thrombolysis Trialists' Collaboration Group. *Lancet*. 2014; published online August 6th, DOI: 10.1016/S0140-6736(14)60584-5. ICH= intracranial hemorrhage

UT Houston Mobile Stroke Unit

- Diagnostic Equipment
  - Portable CT scanner (CereTom)
  - Point-of-care laboratory system
  - Teleradiology/Teleneurology connection

The Need for Speed

Speeding up "Door-to-Needle Time"

Slide courtesy of James Grotta, MD, April 2014.

Endovascular Trials in Acute Ischemic Stroke (AIS)

3 Recent Negative Trials Back to Back to Back

3 Recent Negative Endovascular Trials in AIS

Study	Study Question	Comment
Interventional Management of Stroke III (IMS-III):	Is endovascular therapy after administration of IV t-PA in moderate-to-severe AIS more effective (and safe) compared to IV t-PA alone *within 3 hours* after symptom onset?	Primary Endpoint mRS ≤2: Endovascular 40.8% IV t-PA 38.7% (*P*= 0.70) Predefined Endpoints NIHSS 8-19 or ≥20 (*P*-value= 0.27)
Mechanical Retrieval and REcanalization of Stroke Clots Using Embolectomy (MR RESCUE)	1. Does presence of substantial penumbral tissue predict patients most likely to respond to mechanical embolectomy? 2. Do embolectomy patients have improved functional outcome compared to randomized controls?	*P*= not significant for either question (penumbra or embolectomy)
SYNTHESIS Expansion	AIS patients within 4.5 hours randomized to endovascular therapy (IA thrombolysis with t-PA, mechanical clot disruption or retrieval or a combination of approaches vs. IV tPA)	For mRS (0,1), *P*=.16

Broderick J, et al. *N Engl J Med*. 2013 online February 7, 2013; Kidwell CS, et al. *N Engl J Med*. 2013. DOI: 10.1056/NEJMoa1212793; Ciccone A, et al. *N Engl J Med*. 2013. DOI: 10.1056/NEJMoa1213701; mRS= modfied Rankin score

Criticisms of These Trials

Was the optimal population targeted?

1. Presence of target vessel occlusion?
2. Presence of target salvageable tissue?
3. Fast and effective reperfusion?
4. Other criticisms

Nogueira RG, et al. *Stroke*. 2013;44(11):3272-3274.
Albuquerque FC, et al. *J NeuroInterv Surg*. 2013;5(3):181-183.

Time to Reperfusion and Good Clinical Outcome: Multivariable Model

- Every 30-minute delay in reperfusion results in a 10% relative reduction in a good clinical outcome on the mRS (0 - 2)
- Conclusions
  1. Good clinical outcome associated with angiographic reperfusion with IA therapy that is time dependent
  2. Faster endovascular reperfusion in IMS III may have yielded a positive result (Mean time from onset to IA end/reperfusion: 325 (5 hrs 25 min): range: 180 - 418
  3. Speed of treatment must be emphasized in future reperfusion trials

Khatri P, et al. ISC Platform Presentation February 2013

Better Engineering Leading to Better Results for Recanalization and Reperfusion

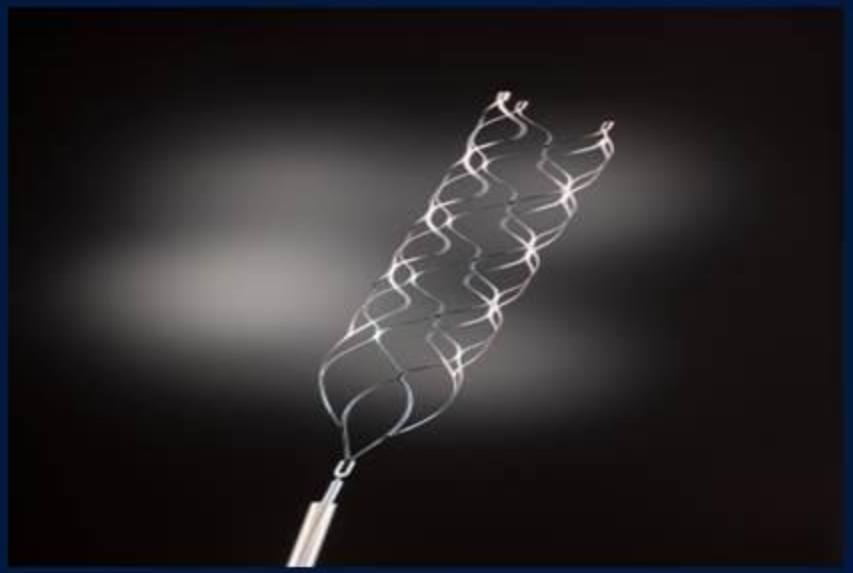
SWIFT and TREVO 2 Trial

“Stent Retrievers”

Solitaire Flow Restoration Device Versus the Merci Retriever in Patients with Acute Ischaemic Stroke (SWIFT): A Randomised, Parallel-group, Non-inferiority Trial

TREVO-2

SWIFT



Saver JL, et al. Lancet. 2012;380(9849):1241-1249.

Current/Future Directions

1. Additional neuroimaging and other factors to better understand the role of:
   A. Collateral blood flow patterns
   B. Clot burden & clot characteristics
   C. Re-visit penumbra & diffusion/perfusion mismatch (volume of infarction vs. tissue at risk), and wake up strokes
   D. Better device technologies
   E. Means to reduce IV t-PA-associated brain hemorrhage
2. Additional trials to prove devices improve efficacy
   A. SWIFT PRIME (IV tPA vs. IV t-PA and the Solitaire device)
   B. Different trial design to answer criticisms

SWIFT PRIME = Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (clinicaltrials.gov NCT01657461)

Summary

1. Intravenous thrombolysis remains 1st line therapy for eligible patients with AIS
2. Treatment in the early time window is important
3. Irrespective of age, stroke severity, and despite an increased risk of fatal ICH early after treatment, alteplase significantly improves odds of a good outcome after stroke within 4.5 hours of administration
4. Clot retrieval devices are available for clinical use according to FDA "clearance" status, however, additional study is needed to prove efficacy and safety of the devices in AIS

Jauch EC, et al. *Stroke*. 2013;44(3):870-947.

Case 1

Determining Eligible Candidates for IV t-PA

Ischemic Stroke Presenting 0 to 3 Hours Post Symptom Onset

Andy S. Jagoda, MD

Specific Objectives

- Review current recommendations for t-PA in patients presenting with acute ischemic stroke within 3 hours of symptom onset
- Discuss imaging options for patients presenting with acute ischemic stroke
- Discuss risk/benefit of patients presenting with mild deficits from an acute ischemic stroke

Case 1

- 28-year-old ballerina presents to the emergency department complaining of acute onset of headache, vomiting, left face numbness, right-sided weakness, and feeling off balance
- Symptoms started 1 hour prior to arrival
- No past medical history
- She was in a minor motor vehicle accident 48 hrs prior
- Medications: Birth control pill

Case 1

- 118/68 mmHg
- 16 breaths/min
- Pulse: 68 beats/min
- pOx: 98%
- Blood glucose 110 mg/dL
- NIHSS 4
  - Mild left-face droop = 1
  - Slight drift on upper and lower right extremity = 2
  - Mild loss of sensation on right face = 1

Question 1: Do you do a HINTS evaluation as part of your neurologic exam in patients with suspected posterior circulation stroke?

1. Yes
2. No
3. I don't know what a HINTS evaluation is

HINTS Testing

- Performed in patients who are symptomatic
- Head Impulse – eyes remain focused on object (vestibular ocular reflex)
  - Normal in stroke
  - Abnormal in peripheral problems (catch up saccades) because the vestibular nerve is not working
- Nystagmus – fast phase change direction in stroke
  - Benign conditions beat in only one direction
  - Central lesions: direction changing nystagmus
- Test of Skew - vertical disconjugate gaze
  - Alternate cover change – avoids fixation

www.emcrit/misc/posterior-stroke-video/

HINTS

- CT misses from 60% to 90% of acute ischemic strokes in the brainstem or cerebellum.
- MRI with diffusion-weighted imaging is more reliable than CT, but still misses from 15% to 20% of patients with posterior circulation stroke in the early period.
- HINTS is reported to be up to 99% sensitive when performed by an experienced clinician

Kuttah JC, et al. *Stroke*. 2009;40(11):3504-3510.

Question 2: Which of the following is the most likely cause of acute ischemic stroke in this 28 year old woman who has no medical problems?

1. Cervical artery dissection
2. Vertebral artery dissection
3. Cocaine abuse
4. Patent foramen ovale
5. Hypercoagulable state due to birth control pill

Question 3: If vertebral artery dissection is considered as the cause of an acute ischemic stroke, what is the emergent imaging of choice?

1. Noncontrast CT
2. CT angio head and neck
3. MRI head
4. MRA head and neck
5. Not sure

Imaging in Acute Ischemic Stroke

- Non-contrast head CT is generally the first test in acute ischemic stroke, but has limitations
- P's of acute stroke imaging: Parenchyma (brain), Pipes (vasculature), Perfusion (blood flow), and Penumbra (at-risk tissue).
- Sequence studies: Non-contrasted head CT, CT angiography (CTA) of the head and neck, and perfusion CT (CTP)
- Enhances the sensitivity of emergent CT neuroimaging for acute ischemic processes
- Identifies patients who may benefit from endovascular interventions

Imaging in Acute Ischemic Stroke

- Emergency imaging of the brain is recommended before initiating any specific therapy to treat acute ischemic stroke (IA).
- CT perfusion and MRI perfusion and diffusion imaging including measures of infarct core and penumbra may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for IV t-PA (IIb).
- Noninvasive imaging of the cervical vessels should be performed routinely as part of the evaluation of patients with suspected TIA (IA).

Jauch EC, et al. *Stroke*. 2013;44(3):870-947.

Question 4: Would you give t-PA to this patient with a NIHSS 4 and a vertebral artery dissection?

1. Yes
2. No
3. Not sure

Minor Stroke: To Lyse or Not To Lyse?

..NO

Relative Exclusion Criteria:

"Only minor or rapidly improving stroke symptoms (clearing spontaneously)"

Jauch EC, et al. *Stroke*. 2013;44(3):870-947.

..YES (?)

NIHSS≤6 better outcome with t-PA **(*P*=0.047)**

Yeo LL. *J Stroke Cerebrovasc Dis*. 2014; 23(8):2156-2162.

BUT...

Treating all mild AIS patients with IV t-PA could potentially save up to $200 million in the USA alone.

Khatri. *Stroke* 2011;2011;42:e66.

ACEP/AAN Clinical Policy: Use of Intravenous t-PA for the Management of Acute Ischemic Stroke in the Emergency Department

- Level A Recommendation: "In order to improve functional outcomes, IV tPA should be offered to acute ischemic stroke patients who meet NINDS inclusion/exclusion criteria and can be treated within 3 hours of symptom onset"*
  - NINDS exclusion: Rapidly improving or minor symptoms

*The effectiveness of t-PA has been less well established in institutions without the systems in place to safely administer the medication

Edlow JA, et al. *Ann Emerg Med*. 2013;61(2):225-243.

AHA / ASA 2013 Recommendation

- Use of intravenous fibrinolysis in patients with conditions of mild stroke deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months, and recent myocardial infarction may be considered and potential increased risk should be weighed against the anticipated benefits (Class IIb, Level C).

Jauch EC, et al. *Stroke*. 2013;44(3):870-947.

Case 1 (continued)

- Patient received t-PA without improvement
- One hour later she became “unresponsive” and unable to move all extremities
- She was able to blink appropriately in response to “yes/no” questions
- Repeat CTA showed no hemorrhage and evidence of basilar artery thrombus

Question 5: At your hospital what would you do?

1. Activate the neuro-interventional team
2. Transfer to a comprehensive stroke center
3. Admit to the ICU
4. Not sure

Case 1 (continued)

- Patient did not receive any additional intervention
- She remains “locked-in” 3 years post event with tracheostomy and peg

Conclusions

- High quality evidence supports the use of t-PA for acute ischemic stroke
- The HINTS evaluation is useful for identifying posterior circulation strokes
- A low NIHSS score is not a contraindication for tPA and risk must be weighed against benefit and quality of life
- Young patients with no history of DM or hypertension, with a normal head CT are at low risk for sICH
- Patients with cervical artery dissection are candidates for tPA if the dissection is extra-cranial
- The role of endovascular interventions for acute ischemic stroke are still being defined

Current Status of Telemedicine in Stroke Care

JOSHUA N. GOLDSTEIN, MD, PHD, FACEP

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How Busy is the Average Emergency Department?

Number of Visits per Year	Number of Emergency Departments
<10k	1718
10-19k	1150
20-29k	822
30-39k	498
40-49k	299
>50k	375

"Higher" Volume EDs

- Proportion of higher-volume (≥8,760 visits/year) EDs differed by region
  - Percentage of high-volume EDs by region, 2001:
    - Southern States: 72% of 1,328 total EDs
    - Midwestern States: 55% of 1,425 total EDs
    - Western States: 66% of 890 total EDs
    - Northeastern States: 89% of 713 total Eds

Sullivan AF, et al. *Ann Emerg Med.* 2006;48(6):694-701.

"Lower" Volume EDs

- Low volume (<8,760 visits/year)
- States with the lowest ED volume (2001):
  - Hawaii
  - South Dakota
  - Utah
- 83% of low-volume EDs were located in a rural setting

Sullivan AF, et al. *Ann Emerg Med.* 2006;48(6):694-701.

Why Telestroke?

- Provides “acute stroke specialist” availability remotely
- Cost effective means to staff a low-frequency, high-impact event
- Concentrate the expertise (high-volume providers but at low-volume sites)
- Standardize care across a range of centers

Advantages of Video Over Telephone

Telestroke

Video:
"Best Gaze"

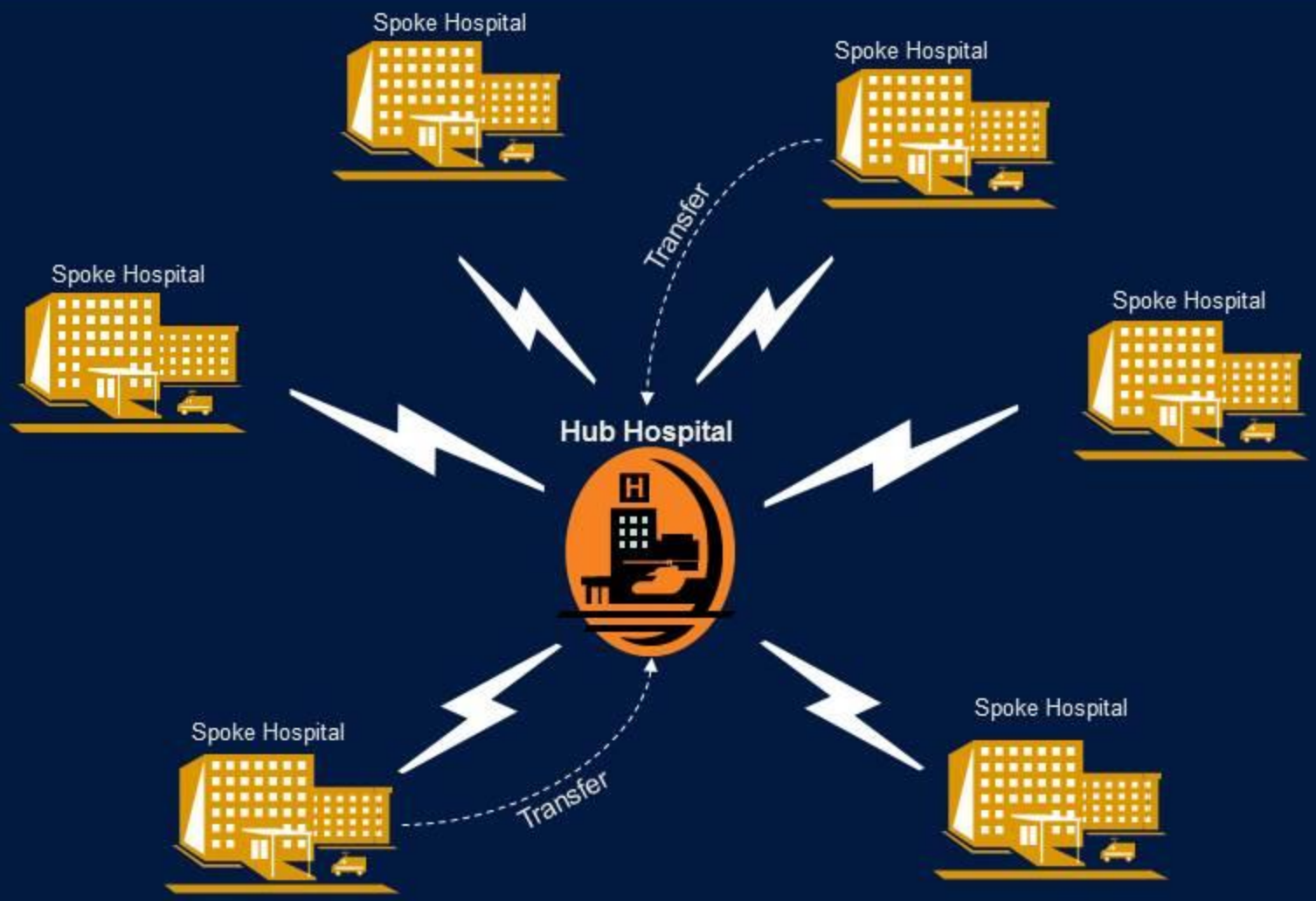
*Video available for download at the "Resources" link for this program

Ability to See Subtle Findings

Video:
"Motor Arm"

*Video available for download at the "Resources" link for this program

The Telestroke "Hub and Spoke" Model



Models of Telestroke Care

- Hospital-based hub and spoke
- For-profit, telemedicine company-based hub and spoke
- Multi-point acute telestroke consult
- Hub-less private practice physicians

Silva GS, et al. Stroke. 2012;43(1):131-136.

Current AHA/ASA Guidelines for Telestroke

- Class I, Level A Recommendations
  - HQ-VTC systems are recommended for performing an NIHSS-telestroke examination in non-acute stroke patients, and this is comparable to an NIHSS-bedside assessment.
  - The NIHSS-telestroke examination, when administered by a stroke specialist using HQ-VTC, is recommended when an NIHSS-bedside assessment by a stroke specialist is not immediately available for patients in the acute stroke setting, and this assessment is comparable to an NIHSS-bedside assessment.
  - FDA approved teleradiology systems are recommended for timely review of brain CT scans in patients with suspected acute stroke.
  - Review of brain CT scans by stroke specialists or radiologists using teleradiology systems approved by the FDA (or equivalent organization) is useful for identifying exclusions for thrombolytic therapy in acute stroke patients.

Schwamm LH, et al. *Stroke*. 2009;40(7):2635-2660.

Current AHA/ASA Guidelines for Telestroke

- Class I, Level of Evidence B
  - In a telestroke network, FDA-approved teleradiology systems can be effective in supporting rapid imaging interpretation in time for thrombolysis decision making.
  - A stroke specialist using HQ-VTC should provide a medical opinion regarding the use of IV t-PA in patients with suspected stroke when on-site stroke expertise is not immediately available.
  - When the lack of local physician stroke expertise is the only barrier to the implementation of inpatient stroke units, telestroke consultation via HQ-VTC is recommended.
  - Assessment of occupational, physical, or speech disability in stroke patients by allied health professionals via HQ-VTC systems using specific standardized assessments is recommended when in-person assessment is impractical.

Schwamm LH, et al. *Stroke*. 2009;40(7):2635-2660.

Current AHA/ASA Guidelines for Telestroke

- Class II, Level of Evidence A
  - HQ-VTC is reasonable for performing a general neurological examination by a remote examiner with inter-rater agreement that is comparable to that between different face-to-face examiners.
- Class IIb, Level of Evidence C
  - Compared with traditional bedside evaluation and use of intravenous t-PA, the safety and efficacy of intravenous t-PA administration based solely on telephone consultation without CT interpretation via teleradiology are not well-established.

Schwamm LH, et al. *Stroke*. 2009;40(7):2635-2660.

Telestroke Challenges

- Financial Sustainability
  - Costs of infrastructure
  - Who is paying?
- Human Resources Sustainability
  - Time and effort on both sides (hub and spoke teams)
  - Licensure and credentialing barriers
  - Can the technology be leveraged to support other purposes including education, networking, etc?

Common Barriers

Imaging

Routine Testing, Reliability of Connections

Stakeholder Buy-In

Getting MDs More Comfortable Using System

Video

Reliability, Image Quality, Routine Testing of Connections, Endpoint Upgrades

Workflow

Improving "Door-to-Needle" Time

Lessons Learned: Best Practices to Consider

- Have a clinical champion at both ends
- Have Emergency Department support
- Standardize clinical care protocols
- "Over" train spoke hospital staff
- Make contingency plans for technology failures
- Sign transfer agreements
- Establish reporting and feedback mechanisms

Challenges to Telemedicine for Stroke

- First and foremost
  - Business model
- Next consideration
  - Hardware
  - Credentialing
  - Backup
  - Secondary services
  - Integration into regional stroke systems of care
  - Integration into other eHealth initiatives

The Future

- Telemedicine from the ambulance?

OPENING THE WINDOW OF TIME IN STROKE THERAPY

New Evidence for the Emergency Department

Course Chair:

ANDY S. JAGODA, MD

Professor and Chair
Department of Emergency Medicine
Mount Sinai School of Medicine
New York, NY