


# Acute Stroke Management: Update

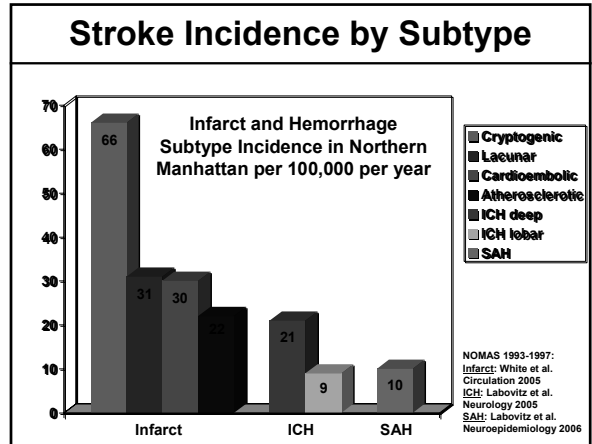
## Daniel Labovitz MD, MS

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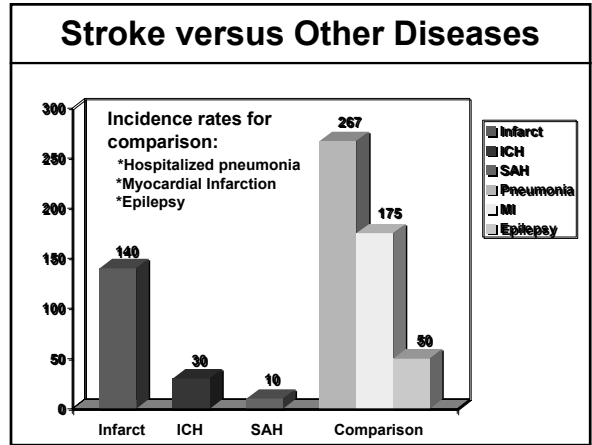


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**Daniel Labovitz MD, MS**  
New York ACEP Scientific Assembly  
July 6<sup>th</sup>, 2006



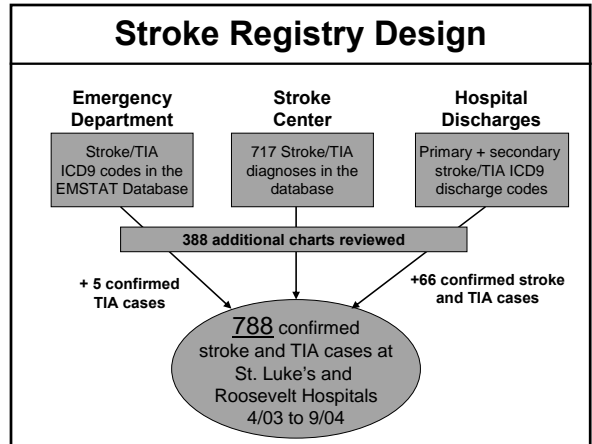
- ### Outline
- **Stroke epidemiology**
    - What is the scale of the problem?
    - Who shows up early for treatment?
  - **NINDS tPA trial: validity and timing**
    - Imbalance in stroke severity between tPA and placebo
    - Phase 4 data
  - **NYS DOH stroke center designation**
  - **Emerging acute infarct therapy**
    - tPA bridging trial: combining IV and intra-arterial tPA delivery
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### Ischemic Stroke Risk Factors

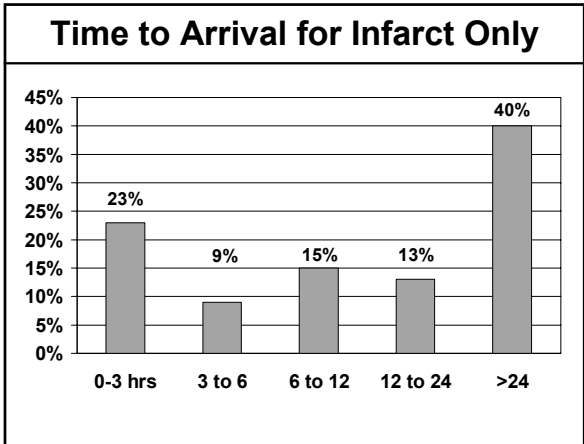
Risk Factor	Prevalence	Relative Risk	Population Attributable Risk
<b>Hypertension</b>			
Age 50	20%	4	40%
Age 60	30	3	35
Age 70	40	2	30
<b>Afib</b>			
Age 50	0.5%	4.0	1.5
Age 60	1.8	2.6	2.8
Age 70	4.8	3.3	9.9
Age 80	8.8	4.5	23.5
<b>Diabetes</b>	7.3	2-6	5-27
<b>Cigarettes</b>	25	1.8	12-18
<b>Cholesterol</b>	25	2.0	15

Adapted from:  
AHA Primary Stroke Prevention Guidelines, Stroke 2006



### Early Arrival by Stroke Subtype

- All cases <3 hours: 35%      P-value
  - Infarct                    23%      Reference
  - ICH                        52        <0.0001
  - TIA                        54        <0.0001
- TIA and ICH cases are more likely to arrive early than infarct cases
  - Probably TIA cases come early or don't come at all
  - Compared to infarct, ICH cases significantly more likely to have:
    - Headache (p<0.0001)
    - impaired consciousness (p<0.0001)
    - NIHSS >15 (p<0.0001)



### Some Will Never Arrive Early

- 789 cases of infarct, TIA and ICH
  - Exclude TIA cases
  - Exclude transfers from outside hospitals
  - Exclude strokes occurring in hospital
- Exclude patients who could not be expected to arrive early in any circumstance
  - Awoke with deficit: 80 cases (15%)
  - Found down: 105 cases (20%)
- 348 cases remain

### Predictors of Early Arrival

Multivariate model: OR >1 favors arriving in < 3 hours\*

	OR	(95% CI)
White	1.0	(reference)
Black	0.8	(0.4-1.5)
Hispanic	0.4	(0.2-0.8)
Other	1.4	(0.5-4.1)
NIHSS 0-7	1.0	(reference)
NIHSS 8-15	2.8	(1.5-5.2)
NIHSS 16+	7.2	(3.4-15.6)
Intracerebral hemorrhage	3.0	(1.6-5.7)
Pre-hospital Rankin 0-2	1.0	(reference)
Pre-hospital Rankin 3-5	0.4	(0.2-0.7)

\*Adjusted for age and sex

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### TOAST Trial: NIHSS and Outcome

- Stroke severity is the most important determinant of longterm outcome
- The NIHSS relationship to outcome is not linear
- Simply "adjusting" for severity with NIHSS in the model as a continuous variable may be misleading

Adams et al. Neurology 1999

### NINDS tPA Trial: NIHSS Imbalance

- The 90-180 minute trial had significant imbalance between placebo and tPA in patients with NIHSS >20 and patients with NIHSS <6

NIHSS	0-90 Minute, n = 302		91-180 Minute, n = 320	
	rt-PA	Placebo	rt-PA	Placebo
No. of patients	157	145	153	167
NIHSS, mean (SD); median	15.2 (7.2); 15	15.0 (6.7); 14	13.5 (7.7); 12	15.4 (6.9); 15
NIHSS groups, percent				
0-5	8.9	6.2	19.0	4.2
6-10	19.1	25.5	24.2	27.5
11-15	24.8	21.4	17.0	21.0
16-20	25.5	25.5	21.6	19.8
>20	22.3	21.4	18.3	27.5

- Some have argued that the imbalance makes the study uninterpretable: Mann. West J Med 2002.

### tPA versus Placebo by NIHSS

- OR > 1 favors tPA. Model is univariate

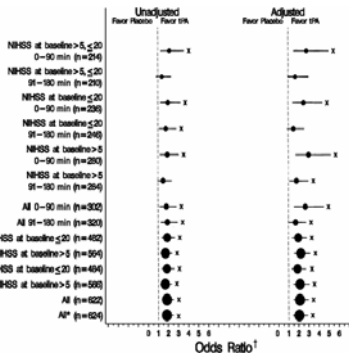
NIHSS	Cases (% good outcome)*		
	tPA	Placebo	OR (95% CI)
0-5	29 (69)	7 (33)	1.3 (0.3-4.5)
5-10	37 (52)	46 (35)	2.0 (1.1-3.9)
11-15	26 (34)	35 (20)	2.1 (0.9-4.6)
16-20	33 (22)	33 (14)	1.7 (0.7-4.0)
>20	28 ( 6)	46 ( 3)	2.5 (0.5-14.4)

\*Good outcome defined as NIHSS = 0 or 1. Other outcome measures not shown but all showed similar benefit

Adapted from Ingall TJ et al. Stroke 2004

### Secondary Analysis of tPA Trial

- Stratified by NIHSS and time to treatment
- Adjusted for known predictors of outcome
- Significant benefit for NIHSS:
  - ≤20
  - ≥5



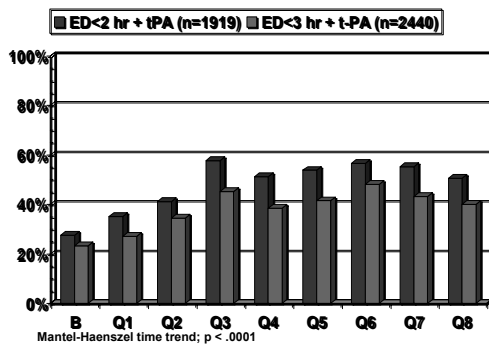
Kwiatkowski T et al. Ann Emerg Med 2005

### Phase 4: Get With The Guidelines

- 65 hospitals who used the web-based patient management tool for 2 consecutive years
- Hospital data included baseline (≥30 records prior to start of GWTG QI phase in 4/03) and 8 consecutive quarters of patient records up to 4/05
- 37,753 clinically identified patients hospitalized with acute ischemic stroke or TIA met these criteria

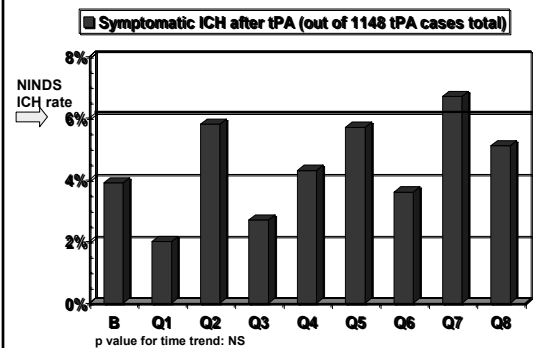
Slide courtesy of the American Heart Association 2/06

### Results -tPA Use Increased



Mantel-Haenszel time trend; p < .0001  
Slide courtesy of the American Heart Association 2/06

### Symptomatic ICH Did Not Increase

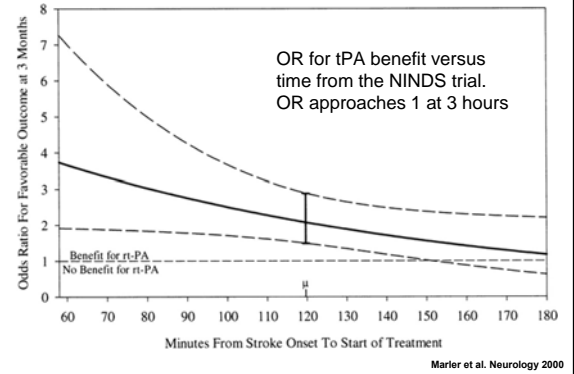


p value for time trend: NS  
Slide courtesy of the American Heart Association 2/06

### Challenging tPA Assumptions

- **Too mild or rapidly improving?**
  - Significant rate of disability at hospital discharge
  - Safest group for tPA Smith E et al. Stroke 2005
  
- **Too large or too severe?**
  - Benefit seen in patients with
    - > 1/3 MCA territory involved on initial CT
    - “Dense MCA sign” Patel et al. JAMA 2001  
Qureshi et al. Stroke 2006
  
- **Too old?**
  - Age does predict disability and death
  - tPA is beneficial in the oldest patients Ingall TJ et al. Stroke 2004

### Time Is Brain



### NY State Dept of Health and tPA

- **Primary Stroke Center designation program**
  
- **911 ambulances are required to deliver acute suspected stroke cases to primary stroke centers**
  - Diversion no greater than 20 minutes
  - Onset < 2 hours
  
- **Based on Brain Attack Coalition guidelines for the establishment of primary stroke centers**
  - Increase tPA use
  - Improve acute stroke care

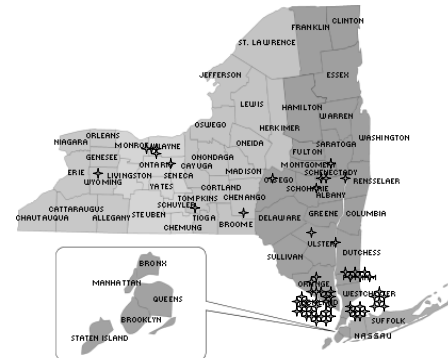
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### Requirements for Certification

- **24/7 stroke team able to see patient within 15 min**
  - No neurologist required
  - ED staff play a critical role
  - 8 hours of CME stroke education per year
- **CT available 24/7**
- **Neurosurgery available within 2 hours**
- **Written stroke protocols**
- **Center maintains a database for QA**

### NY State DOH Stroke Centers



### Rural Stroke Centers?

- By May 2006, the DOH had certified 85 centers
- Most hospitals that have not applied are rural
  - >50% have no neurologist on staff
  - 5 counties have no hospital
  - 18 counties have only 1 hospital
- The state is exploring a “telestroke” solution

### The STroKE DOC System

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### IV tPA Chased by Intra-arterial tPA

- NINDS “Interventional Management of Stroke” trial
  - Multi-center, open-label, single arm trial of IV tPA followed by intra-arterial (IA) tPA
    - 0.6 mg/kg tPA by IV with 15% bolus
    - 22 mg IA tPA delivered over 2 hours
  - Minimum NIHSS: 10
  - IV tPA to start within 3 hours of stroke onset
    - Mean time to start IV tPA: 140 minutes
    - Mean time to start IA tPA: 231 minutes
  - 80 patients enrolled
- Similar ICH rate to NINDS tPA trial with similar benefit. Proving benefit over IV tPA will be hard

IMS Study Investigators. Stroke 2004

### Mechanical Embolectomy

- MERCI Trial
  - Single-arm, multi-center safety trial
  - Historical controls
  - Excluded patients eligible for tPA
- 8-hour window
- 151 patients enrolled
  - 46% recanalized
  - 8% had symptomatic ICH
  - 7% had “significant procedural complications”
- Benefit?

Smith WS et al. Stroke 2005

### Neuroprotection: SAINT-1 Trial

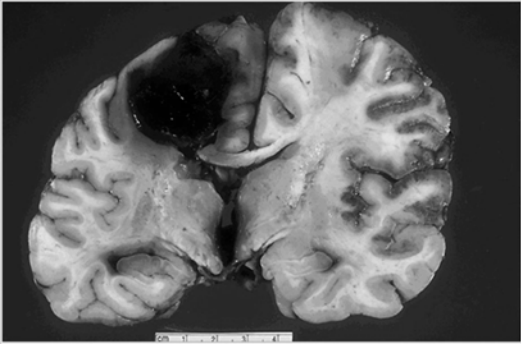
- NXY-059 is a free-radical scavenger
- Randomized, double-blind placebo-controlled trial
- Eligibility
  - NIHSS >6
  - Limb-weakness
  - Infarct onset < 6 hours
- 1699 patients completed the trial
  - Significant benefit in primary measure: Rankin at 90 days (OR 1.20 95% CI 1.01-1.42)
  - No benefit in NIHSS score
  - In the subgroup of 489 patients treated with IV tPA, those who received NXY-059 had a significantly lower hemorrhagic conversion rate

Lees KR et al. NEJM 2006

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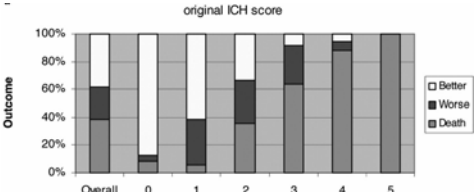
### ICH 30-Day Mortality: 30-50%



### ICH Score: Predicting Mortality

Predictor	Points	Each element in the score is an independent predictor of 30-day mortality
GCS 3-4	2	Score range: 0-6
5-13	1	
ICH volume	1	
Intraventricular blood	1	
Infratentorial origin	1	
Age >80	1	

original ICH score



Godoy, D. A. et al. Stroke 2006

### AHA Guidelines: ICH Management

- **No Steroids**  
(Level II, Grade B)
- **Keep head of bed elevated >30 degrees**
- **Use ICP monitor for elevated ICP and GCS<9**  
(Level V, Grade C)
- **Hyperventilation and mannitol for ICP>20**  
(Level V, Grade C)
- **Ventricular drain for hydrocephalus**  
(Level V, Grade C)

### AHA Management Guidelines

- **Blood pressure: maintain MAP<130, give pressors for SBP<90**  
Level V, Grade C
  - Unproven relationship to risk of hemorrhage expansion in 24 hours
  - Concern about perfusion of ischemic penumbra (existence of which remains controversial)

### AHA Management Guidelines

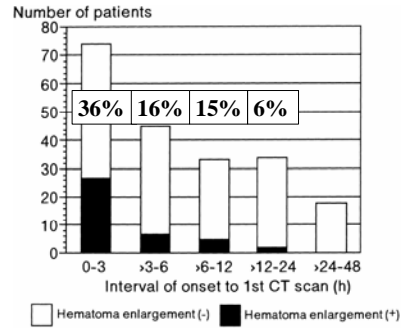
- **Surgery is indicated for cerebellar ICH >3 cm with neurological deterioration or hydrocephalus**  
Level III, grade C

### Early Hematoma Expansion

- Prospective observational study of ICH patients with first CT within 3 hours of onset
  - 103 patients had repeat CTs performed 1 hour and 20 hours after initial CT
- 38% had >33% volume expansion within 24 hours
- No clinical or CT predictor of hematoma expansion identified

Broderick et al. Stroke 1997

### Early Expansion: How Long?



- 298 ICH cases scanned within 48 hours and again within 5 days
- Hematoma expansion defined as >40% or >12.5 cm<sup>3</sup>

Kazui S et al. Stroke 1996

### Factor VII for Acute ICH

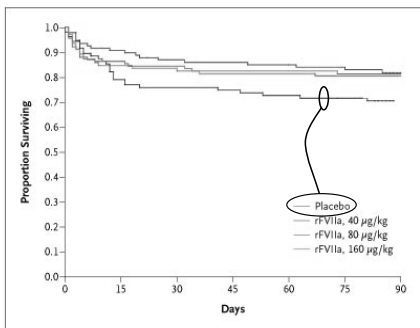
- Approved for use in hemophiliacs with antibodies to Factor VIII (2 min IV infusion)
- Chest guidelines for warfarin-related hemorrhage include use of Factor VII but dosing unclear
- Nova 7 Trial
  - Phase 2 trial for ICH (not on warfarin)
  - Goal: prevent early hemorrhage expansion >33%
  - 399 patients with ICH within 3 hours of onset randomized to placebo, 40, 80, or 160 mcg/kg
  - Treatment initiated within 4 hours of onset

Mayer SA, et al. NEJM 2005

### Effect on Hematoma Expansion

- Mean volume expansion at 24 hours:
  - Placebo: 29%
  - 40 mcg 16
  - 80 mcg 14
  - 160 mcg 11
- Timing matters for volume expansion:
  - Treatment 0-3 hours: placebo 34%, treated 14%
  - Treatment 3-4 hours: placebo 14%, treated 16%

### Nova 7 Trial: 90 Day Survival



### Assorted Outcome Measures

rFVIIa	Modified Rankin Scale				Barthel Index			
	0-1	2-3	4-5	Dead	95-100	55-90	0-50	Dead
160 µg/kg	24	21	35	19	37	15	29	19
80 µg/kg	21	29	30	18	36	19	27	18
40 µg/kg	17	29	37	18	27	24	31	18
Placebo	8	23	40	29	22	17	32	29

percent of group

rFVIIa	Extended Glasgow Outcome Scale				NIH Stroke Scale			
	7-8	5-6	2-4	Dead	0-1	2-8	≥9	Dead
160 µg/kg	15	11	55	19	18	40	22	19
80 µg/kg	13	15	53	18	21	40	20	18
40 µg/kg	11	16	55	18	10	51	22	18
Placebo	6	12	52	29	13	29	29	29

percent of group

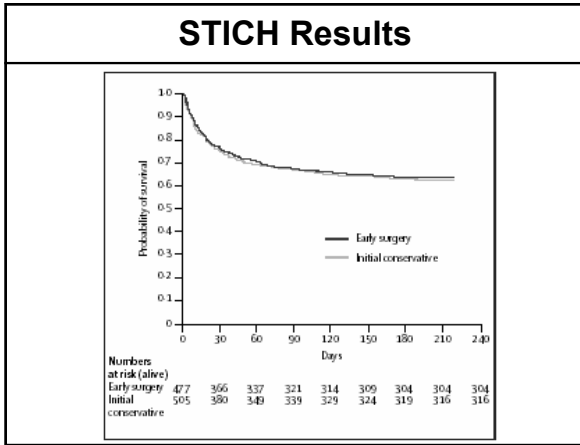
### Complications

- **Thromboembolic events**
  - Placebo: 2% venous, 0% arterial
  - Factor VII: 2% venous, 5% arterial
    - 9 cerebral infarcts (2 fatal, 5 disabling)
    - 7 myocardial infarcts (1 clinically significant)
  - Almost all events occurred within 4 days of treatment

### STICH Trial

- **Multicenter international randomized trial of early surgery versus medical management for ICH**
  - Crossover to surgery possible, so NOT strictly a trial of surgery versus medicine
  - Surgeon uncertain about benefit of surgery
  - Randomization within 72 hours of ICH; surgery within 24 hours of randomization
  - Supratentorial ICH only
- **1033 patients randomized**

Mendelow et al. Lancet 2005



### Conclusions

- **Early arrival depends on stroke severity, subtype, the type of symptoms and (perhaps) ethnicity**
- **tPA is effective regardless of stroke severity but requires a multi-disciplinary team approach**
  - Its time to stop complaining about the trial
  - Its time to start working together to devise programs to use tPA safely
  - Most of us will not have another acute intervention available for years to come
- **ICH expansion is lethal but may soon be treatable**