
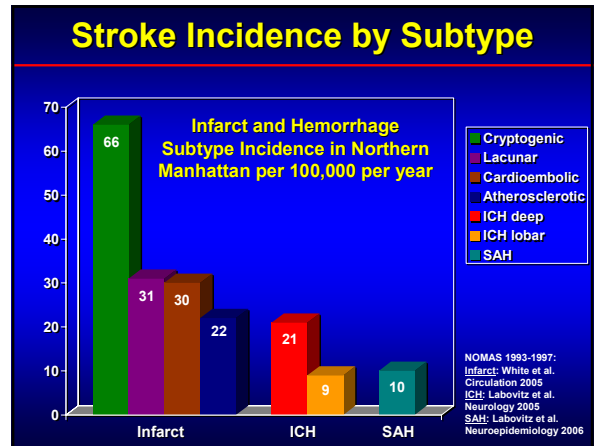


Acute Stroke Management: Update

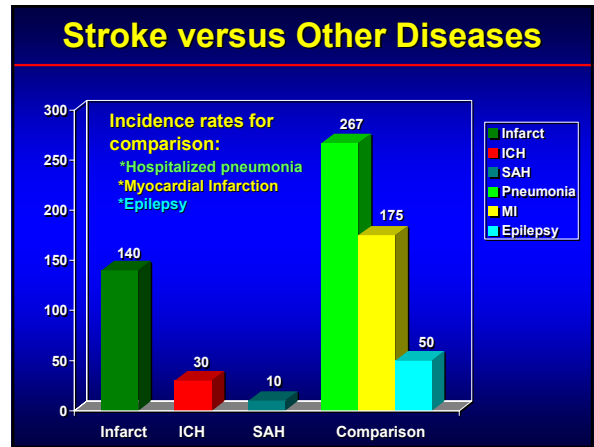


**New York University
School of Medicine**
 Department of Neurology
 Division of Cerebrovascular Disease

Daniel Labovitz MD, MS
 New York ACEP Scientific Assembly
 July 6th, 2006



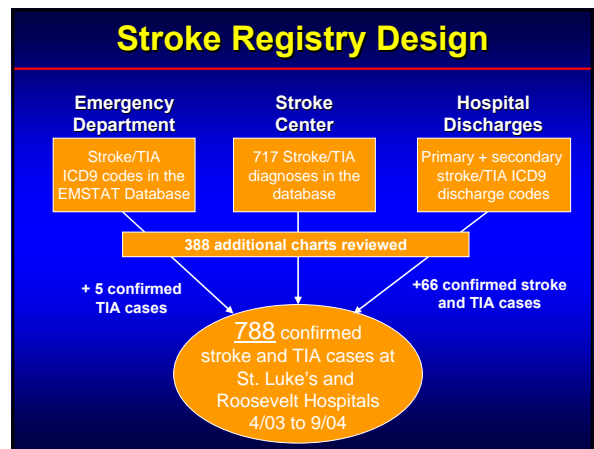
- ### Outline
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Ischemic Stroke Risk Factors

Risk Factor	Prevalence	Relative Risk	Population Attributable Risk
Hypertension			
Age 50	20%	4	40%
Age 60	30	3	35
Age 70	40	2	30
Afib			
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
Diabetes	7.3	2-6	5-27
Cigarettes	25	1.8	12-18
Cholesterol	25	2.0	15

Adapted from: AHA Primary Stroke Prevention Guidelines, Stroke 2006

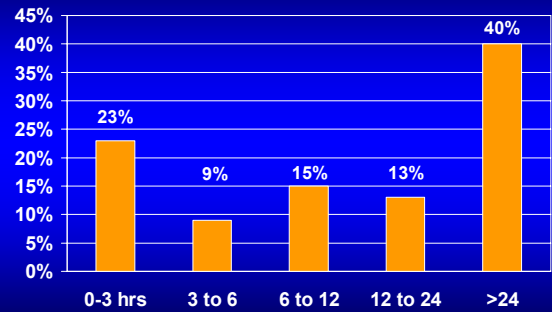


Early Arrival by Stroke Subtype

- **All cases <3 hours: 35%**

Stroke Subtype	Percentage	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)

Time to Arrival for Infarct Only



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*

Predictor	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)

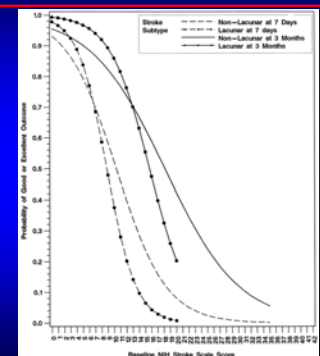
*Adjusted for age and sex

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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	6.3	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

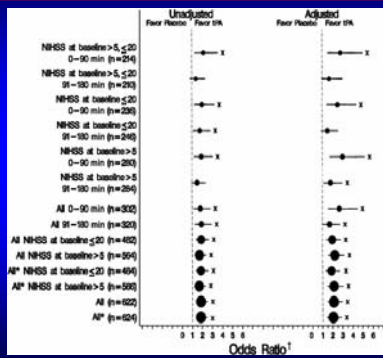
NIHSS	Cases (% good outcome)*		
	tPA	Placebo	OR (95% CI)
0-5	29 (69)	7 (33)	1.3 (0.3-4.5)
5-10	37 (52)	46 (35)	2.0 (1.1-3.9)
11-15	26 (34)	35 (20)	2.1 (0.9-4.6)
16-20	33 (22)	33 (14)	1.7 (0.7-4.0)
>20	28 (6)	46 (3)	2.5 (0.5-14.4)

*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

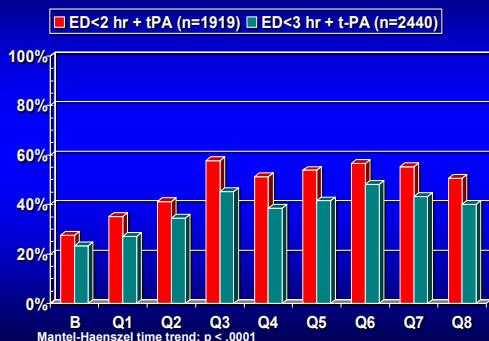


Phase 4: Get With The Guidelines

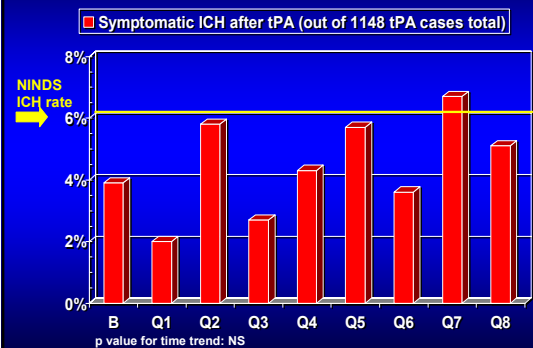
- 65 hospitals who used the web-based patient management tool for 2 consecutive years
- Hospital data included baseline (≥30 records prior to start of GWTG QI phase in 4/03) and 8 consecutive quarters of patient records up to 4/05
- 37,753 clinically identified patients hospitalized with acute ischemic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

Slide courtesy of the American Heart Association 2/06

Results –tPA Use Increased



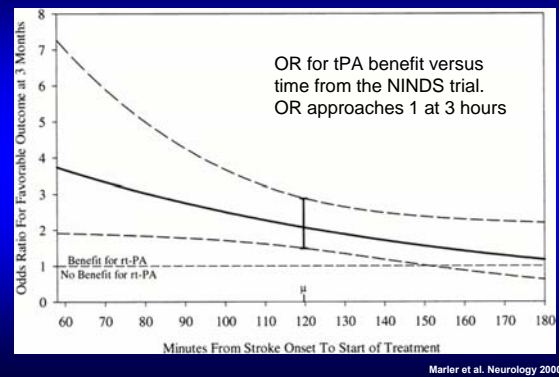
Symptomatic ICH Did Not Increase



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

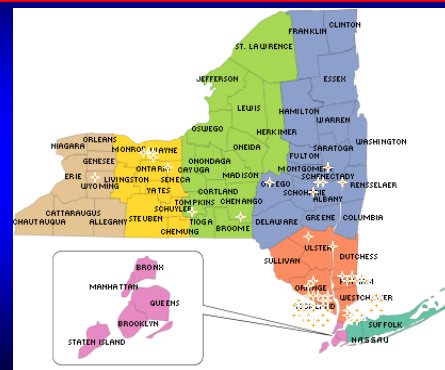
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Requirements for Certification

- **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**

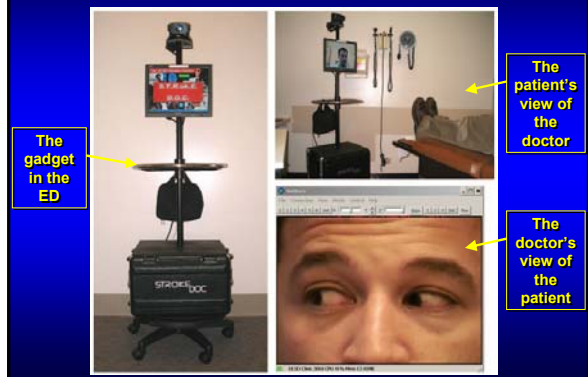
NY State DOH Stroke Centers



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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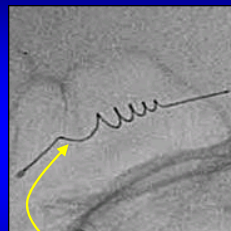
IV tPA Chased by Intra-arterial tPA

- **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

- **MERC1 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

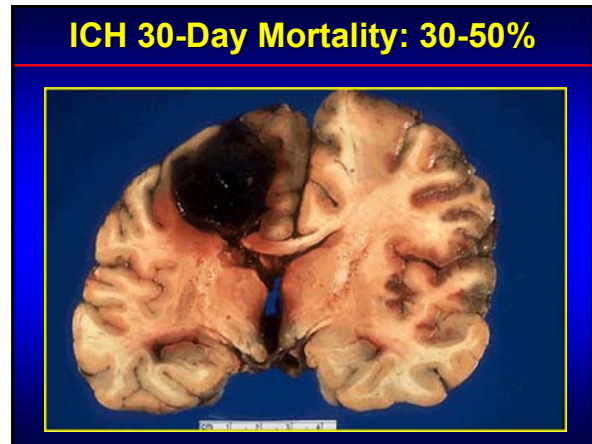
Neuroprotection: SAINT-1 Trial

- **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 Score: Predicting Mortality

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

Godov, 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

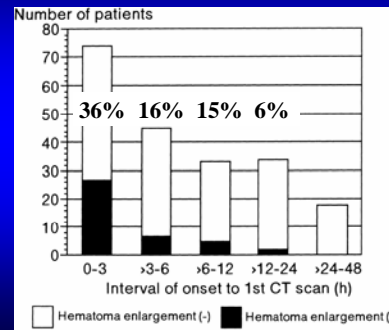
- **Surgery is indicated for cerebellar ICH >3 cm with neurological deterioration or hydrocephalus**
Level III, grade C

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 cm³**

Kazui S et al. Stroke 1996

Factor VII for Acute ICH

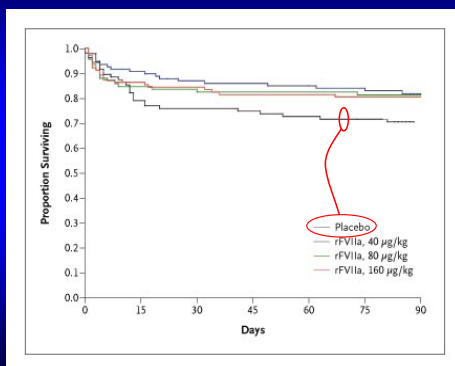
- **Approved for use in hemophiliacs with antibodies to Factor VIII (2 min IV infusion)**
- **Chest guidelines for warfarin-related hemorrhage include use of Factor VII but dosing unclear**
- **Nova 7 Trial**
 - Phase 2 trial for ICH (not on warfarin)
 - Goal: prevent early hemorrhage expansion >33%
 - 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

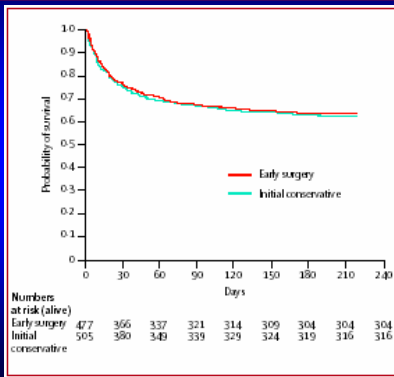
- **Thromboembolic events**
 - Placebo: 2% venous, 0% arterial
 - Factor VII: 2% venous, 5% arterial
 - 9 cerebral infarcts (2 fatal, 5 disabling)
 - 7 myocardial infarcts (1 clinically significant)
 - Almost all events occurred within 4 days of treatment

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

STICH Results



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**