Expanding Treatment Opportunities in Acute Ischemic Stroke

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Treatment of Acute Ischemic Stroke 2015

- Alteplase remains the only FDA approved medical therapy for Acute Ischemic Stroke (AIS)
- Despite availability since 1996 the US treatment rate is an abysmal 2.4% nationally

Reasons patients do not receive IV-tPA for AIS

- Delayed/Unknown time to presentation 40-75%
- Symptoms too mild or rapidly improving 20-43%
- Elevated BP 5-10%
- Medical/surgical history (ie. Age) 5-10%
- Laboratory abnormalities 5-10%

Opportunities for expanding treatment of AIS with IV-tPA

- SITS-MOST study addresses continued concern of providers regarding safety and efficacy of IV-tPA for AIS
- More patients may qualify with extended time window to 4.5 hrs with ECASS 3 study
- Experience in US and EU demonstrates safety and efficacy of IV-tPA <4.5 hrs in routine clinical practice
- Clarifying inclusion/exclusion criteria re: Age ≥80, Rapidly Improving or Minor Symptoms(RIMS)
- Medicolegal precedent surrounding failure to treat stroke victims with IV-tPA

US Geographic Distribution of rt-PA Utilization by Hospital for Acute Ischemic Stroke

Kleindorfer Stroke. 2009;40:3580.

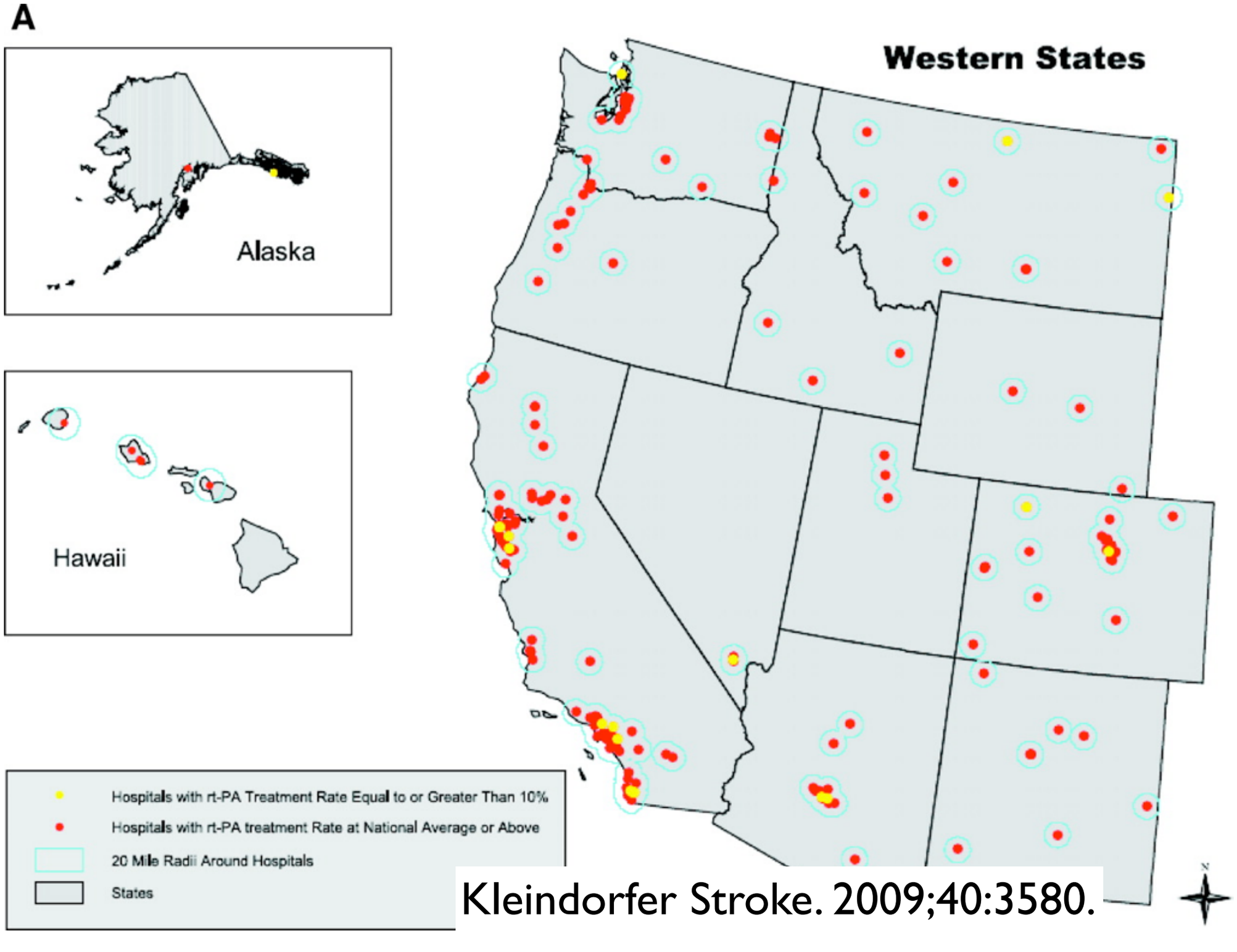
- MEDPAR database, a claims-based dataset that contains every fee-for-service Medicare-eligible hospital discharge in the US
- Searched stroke DRGs 014,015 and 559, ICD-9 433,434,439 and thrombolysis code 99.1
- 4750 hospitals 495,186 ischemic strokes '05-'07
- 2.4% of all ischemic strokes received tPA (11,884/495,186)

US Geographic Distribution of rt-PA Utilization by Hospital for Acute Ischemic Stroke

Kleindorfer Stroke. 2009;40:3580.

- Treatment rates varied from 0-23%
- 16.9% hospitals reported treatments >2.4%
- 64.2% of hospitals reported no tPA treatments
- Hospitals that reported no rt-PA use were smaller hospitals with an average bed size of 95, located in less densely populated areas
- 40% of US population resides in counties with <2.4%

Western States tPA Treatment Rates



Kleindorfer Stroke. 2009;40:3580.

Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)

Lancet 2007; 360: 275-82

SITS-MOST design

Lancet 2007; 360: 275-82

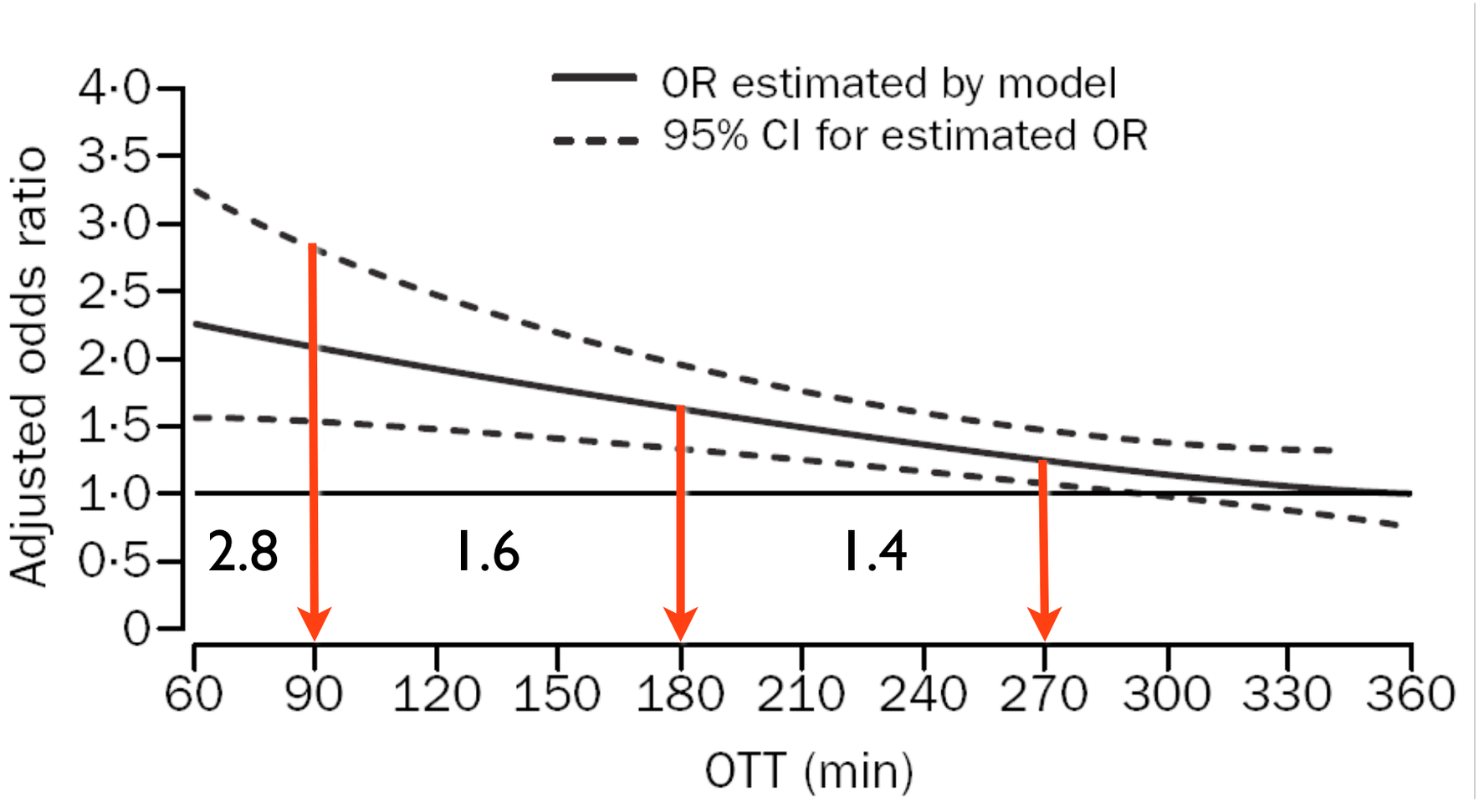
- 6483 patients <u>received</u> 0.9 mg/kg IV tPA <3 hrs
- 285 Centers; 14 countries; 3.5 yrs
- Prospective, open, monitored observational registry

Worldwide Experience with IV-tPA for AIS (<3hrs)

Study	N	Sites	Patient Profiles	Onset to Tx'd	Outcomes		
					mRS≤2	SICH	Death
NINDS tPA Tx'd	310	40	68yrs	42% 80-90'	49%	6.4%	17%
		US only	NIHSS 14	42% >120'			
SITS-MOST	6,483	285	68yrs	11% <90'	55%	7.3%	11%
		14 EU	NIHSS 12	66%>120'			

Extended IV-tPA Treatment Window for AIS

Pooled Analysis of ATLANTIS, ECASS and NINDS IV tPA Trials



Hacke, Lancet: 2004: 9411: 768-74

European Cooperative Acute Stroke Study (ECASS 3)

NEJM 2008;359:1317-29

- 130 sites 19 European Countries
- 821 patients randomized to Alteplase (418) or placebo (408) from 2003-2007
- 0.9mg/kg IV t-PA total (10%/1 min;90%/1 hour)

ECASS-3 Main Inclusion Criteria

NEJM 2008;359:1317-29

- Acute ischemic stroke
- Age, 18 to 80 years
- Onset of stroke symptoms 3 to 4.5 hours before initiation of study drug administration
- Stroke symptoms present for at least 30 minutes with no significant improvement before treatment

ECASS-3 Main Exclusion Criteria

- Intracranial hemorrhage
- Time of symptom onset unknown
- Symptoms rapidly improving or only minor before start of infusion
- Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques
- Seizure at the onset of stroke
- Stroke or serious head trauma within the previous 3 months
- Combination of previous stroke and diabetes mellitus
- Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial thromboplastin time at presentation exceeding the upper limit of the normal range
- Platelet count of less than 100,000 per cubic millimeter
- Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits
- Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter
- Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal
- Oral anticoagulant treatment
- Major surgery or severe trauma within the previous 3 months
- Other major disorders associated with an increased risk of bleeding

ECASS-3 Main Exclusion Criteria

- Age > 80
- Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques
- Combination of previous stroke and diabetes mellitus
- Oral anticoagulant treatment

European Cooperative Acute Stroke Study (ECASS 3)

NEJM 2008;359:1317-29

- Treatment with IV t-PA associated with a 1.34 odds of independent outcome (mRS 0, 1) at 90 days
- Intracranial hemorrhage greater in t-PA treated(27%) vs. placebo (17%)
- Symptomatic: t-PA (2.4%) vs. placebo (0.3%)
- Mortality: t-PA (7.7%) vs. placebo (8.4%)

NINDS 0-3 hrs vs. ECASS 3 3-4.5 hrs IV-tPA

	NIHSS	Favorable Outcome (Odds Ratio)	Symptomatic ICH	Mortality (vs. placebo)
NINDS 0-90 min	14	2.81	6.4	17% vs 21%
NINDS 90-180 min		1.55		
ECASS 3 median 3:59 min	9	1.34	7.9	7.7% vs 8.4%

Safety and Efficacy of IV-tPA within 4.5 hrs in Clinical Practice in US and EU

US Experience with tPA from the AHA/ASA Get With the Guidelines Stroke registry

JAMA. 2013;309(23):2480-2488

- 1.2 M US patients with Acute Ischemic Stroke reviewed 2003-2012 in 1395 US hospitals
- 58,353 (5.8%) patients treated w/ IV t-PA within 4.5 hr time window (7920 treated 3-4.5 hrs)
- Medians 72 y/o; 144 min Door-to-Needle; NIHSS 12
- 33% independent in ambulation;39% discharged home
- 4.9% Symptomatic intracranial hemorrhage

Safe implementation of Treatments in Stroke (SITS) International Stroke Thrombolysis Register

SITS-ISTR

Lancet Neurol 2010 Sep;9(9):866-74

- 23,942 patients received 0.9 mg/kg IV tPA <4.5 hrs (2376 patients in 3-4.5hrs)
- 669 Centers; 34 countries; 8 yrs
- Using SITS-MOST definition SICH 1.8%(vs. 7.4% in NINDS)
- No differences in Mortality or SICH and ~60% achieved functional independence at 3 months

AHA/ASA Science Advisory

Stroke 2009;40:2945

- rtPA should be administered to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke (Class I Recommendation, Level of Evidence B).
- The eligibility criteria for treatment in this time period are similar to those for persons treated at earlier time periods, with any one of the following additional exclusion criteria: Patients older than 80 years, those taking oral anticoagulants (regardless of INR), those with a baseline National Institutes of Health Stroke Scale score >25, or those with both a history of stroke and diabetes

Rapidly Improving/Mild Symptoms (RIMS) Exclusion from IV-tPA

Rapidly Improving/Mild Symptoms (RIMS) Exclusion from IV-tPA

- ATLANTIS, NINDS, ECASS protocols excluded AIS patients with RIMS
- Significant proportion of patients presenting in time for treatment but excluded due to RIMS have early neurologic deterioration and very poor outcomes
- Neurologic deterioration is associated with persistent large vessel occlusion (LVO)
- AIS patients with LVO have higher risk of death and disability
- Patients with RIMS and LVO should be considered for treatment

Significant proportion of AIS patients presenting in time for treatment but excluded due to RIMS are dead or dependent at discharge

	AIS ≤ 3 hrs	Excluded- too mild/improved	Dependent or dead	Large Vessel Occlusion
Kleindorfer 2004	406	174 (43%)		
Barber 2001	314	98 (31%)	31 (32%)	
Smith 2005	128	41 (34%)	11 (27%)	4 (36%)
	AIS ≤ 6 hrs			
Rajajee 2006	74	39(53%)	8 (21%)	4 (50%)

Neurologic deterioration is associated with persistent large vessel occlusion (LVO)

	AIS ≤ 3	RIMS	Neurologic Deterioration	Large Vessel Occlusion
Smith 2005	128	41 (34%)	7 (17%)	4 (57%)
	AIS ≤ 6 hrs			
Rajajee 2006	74	39	4 (10%)	3 (75%)
Alexandrov 2000	50	50	8 (16%)	5 (62%)

AIS patients with LVO have higher risk of death and disability

W. Smith Stroke 2009;40:3834-40

- 575 consecutive stroke and TIA presenting <24 hr to MGH and UCSF underwent CT/CTA arch to COW
- LVO seen in 46% strokes and 13% TIAs
- Age, baseline NIHSS and gender strongly predictive of outcome and mortality
- Presence of LVO on CTA associated with 4.5 fold increased odds of death and 3 fold reduction in odds of good outcome

Treatment of patients with rapidly improving or mild symptoms (RIMS) appears safe and effective

	RIMS Treated w/ IVtPA	Admit NIHSS	Functional Outcome	SICH/ASICH
Baumann 2006	19	5	95% mRS 0 (1 death)	0/21%
Kohrmann 2009	32	<4	94%mRS 0-1 47% mRS 0	0/3%

Use of CTA in evaluation of Acute Ischemic Stroke

- Hi Sensitivity in detection of LVO
- Presence of LVO useful for
    - determining need for further intervention w/ or w/o IV-tPA;
    - may result in treatment in RIMS patients

Use of IV-tPA in Treatment of Acute Ischemic Stroke (AIS) in Elderly Age >80

People Fear Stroke the Greatest

Many elderly would rather die than be alive and severely disabled. [1]

- 45%-69% of stroke patients considered stroke to be a worse outcome than death. [1-3]

- >80% of elderly population without stroke considered death preferable to severe disability. [2]

1. Samsa GP Am Heart J 1998;136:703
2. Hanger HC Clin Rehabil. 2000 Aug;14(4):417
3. Solomon NA Stroke 1994 Sep;25(9):1721

Use of IV-tPA for AIS in age ≥ 80

- ≥80 age group accounts for 30-37% of all ischemic stroke
- While stroke is more common in old age, elderly have been underrepresented (13% in NINDS) or excluded from RCTs for IV-tPA use in AIS (ATLANTIS;ECASS-3)
- Increasing age is associated with higher in-hospital mortality and sICH
- The few studies comparing IV-tPA treated stroke patients age >80 have had inconsistent findings re: favorable outcome and sICH

Intravenous thrombolysis in stroke patients of ≥80 versus <80 years of age—a systematic review across cohort studies

- Systematic review of 6 cohort studies using individual patient data for 2,244 patients; 477(21%) ≥ 80 years
- Stroke patients of ≥80 years receiving rtPA have a substantially higher mortality risk than younger patients and were less likely to recover favorably
- The risk of symptomatic ICH is similar in both the age groups

Age and Ageing 2006; 35: 572–580

Use of IV-tPA for AIS in age ≥ 80

- Baseline characteristics in elderly predispose to poorer outcomes:
  - Female sex
  - HTN and cardiac comorbidities
  - more severe NIHSS
- Elderly have least to lose given significant risk of poor outcome without IV-tPA and lack of elevated risk of sICH with IV-tPA

ED providers medicolegal concerns with use of tPA

Empirical Characteristics of Litigation Involving Tissue Plasminogen Activator and Ischemic Stroke

- 33 cases identified in legal databases
- Verdicts: 21 defendant (64%); 12 plaintiff (2 settled; 1 arbitrated)
- physician defendants 19 cases ED; 6 cases Neurologist and ED providers
- 22 cases involved patients presenting to ED and ED provider's evaluation and treatment were at issue; 10 of these were without Neurology consultation

Ann Emerg Med. 2008;52:160-164

Empirical Characteristics of Litigation Involving Tissue Plasminogen Activator and Ischemic Stroke

- 29(88%) cases plaintiffs claimed failure of treating physician to provide tPA
- 3(9%) claimed that use of tPA caused injury
- 10/12(83%) plaintiff verdicts claimed failure to receive tPA caused injury
- Liability range $100k-$30M average $5.6M

Ann Emerg Med. 2008;52:160-164

Medicolegal considerations with intravenous tissue plasminogen activator in stroke: a systematic review

- 40 case descriptions identified in legal databases
- 38/40 (95%) claimed related to failure to administer tPA
- Verdicts 65% favored defendant 30% favored plaintiff
- ED physicians involved in 60.5%; Neurologists in 20%

Bhatt et. al.Stroke Res Treat. 2013;2013

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Summary

- Treatment rates for AIS in US remain low
- AIS patient may now receive treatment in 3-4.5 hour time window
- Patients with Age >80 and Minor NIHSS with disabling symptoms should receive IV-tPA
- CTA is useful in determining need for interventional therapy and can guide management in those that may not qualify based on low NIHSS.
- Patients that do not qualify for IV-tPA after informed verbal consent and consultation with stroke neurologist should have clear documentation in medical record