



## **Thrombolytic Therapy in Stroke: A Critical Analysis of the Evidence**

The use of thrombolytics in acute stroke patients is an area of significant controversy. Some important questions need to be answered by emergency physicians to include what is the benefit of thrombolysis in management of acute stroke patients, which patients should receive thrombolysis, what are the responsibilities of the physician. This lecture will review the current literature on this topic and help physicians determine whether this treatment modality should be used in their clinical setting.

- Evaluate current research to determine the patient population in your clinical practice eligible for thrombolysis.
- Apply evidence from current research to your clinical practice in treating patients with acute stroke.

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### **FACULTY**

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## Thrombolytic Therapy in Stroke: A Critical Analysis of the Evidence

### I. Course Description:

- A. There is uncertainty whether IV thrombolytics should be used in the treatment of acute ischemic stroke.
- B. This course will:
  - 1. develop a model for understanding the benefits, harms and costs of thrombolysis in stroke.
  - 2. use the literature to examine and characterize each of the elements in the model
  - 3. assess the overall outcomes of the model
  - 4. anticipate future research and likely developments in the treatment of stroke

### II. Objectives:

At the conclusion of this course, participants will be able to:

- A. Sketch out a model for understanding the key elements in the thrombolysis-in-stroke debate.
- B. Understand the underlying each of the elements in the model.
- C. Understand how each of the elements combines in an overall assessment of the problem.
- D. Understand the problems incurred when analyzing the literature for this purpose.
- E. Explain the main elements in the evidence-based medicine analytic process.

### III. Course Outline

#### A. Background

- 1. Stroke is unquestionably a prevalent and devastating disease
  - a. 500,000 strokes per annum in U.S.
  - b. 3<sup>rd</sup> leading cause of death
  - c. leading cause of permanent disability
    - quality of life decreased by hemiparesis, aphasia, inability to walk and over 50% of victims have one of these
- 2. Prevention (risk factor reduction) remains the most important goal
- 3. Types of stroke:
  - Hemorrhagic = 15%      versus      Ischemic = 85%

## B. The Model

### 1. Version 1 (in temporal order)

- a. Stroke symptoms begin
- b. Patient (or onlooker) notices symptoms and signs
- c. Patient (or onlooker) identifies symptoms and signs as potential stroke
- d. Patient (or onlooker) makes contact with health care system
- e. Health care system reacts promptly
- f. Physical examination to identify stroke and rule-out mimickers
- g. CT scan to rule out bleeding (and possibly large infarction)
- h. CT scan read by qualified reader
- i. Administration of medication (thrombolytic at present)
- j. The medication has to be efficacious
- k. All of the above must occur within "x" hours

### 2. Version 2 (in order of importance)

*Efficacy – performance of the agent under ideal circumstances*

*Effectiveness – **performance** of the agent under actual conditions*

*Efficiency – (and cost-effectiveness) how well the program works in contrast to other health programs*

#### Issues of efficacy

- a. Agent has to be efficacious  
If we do not have an agent that works (produces better outcomes than placebo) then all else is moot.

#### issues of effectiveness

- b. Patient must be having a stroke  
The history and physical must be sufficiently specific to ensure that patients with other conditions are not inadvertently given the drug. Stroke mimics that typically do not produce abnormalities on CT (e.g. Todd's paralysis s/p seizure) must be identified clinically
- c. The CT scan must be read correctly  
Thrombolytic agents can kill if given in the setting of hemorrhagic stroke. Any benefit from thrombolysis for those in the population with ischemic stroke could be erased or overrun should patients with hemorrhagic stroke inadvertently receive the drug.
- d. Timing must be correctly ascertained  
While we debate whether the cutoff for thrombolysis should be 90 minutes, 3 hours, 4 hours or 6 hours, there is agreement that there is an upper limit. Whatever cutoff is supported by the literature, care must be taken to exclude those who are beyond this time point.

## Issues of Efficiency

Factors that affect the percentage of eligible patients

- e. Patients must know they are having a stroke and promptly present for care, since therapy must be administered rapidly.
- f. Patients must receive the proper advice when they contact the health care system.  
Primary providers must recognize stroke symptoms as an emergency.
- g. **The** emergency system must provide rapid: evaluation, cranial CT, CT reading and treatment.
- h. The patient must have an ischemic stroke that meets eligibility criteria for treatment.

C. Filling in the model

1. We will work off Version 2 (order of importance)

2. Issues of Efficacy

We use an evidence-based approach

- a. Medline search - **find** all **RCTs**
- b. Systematically analyze these **RCTs** [see attached matrix for summary of the studies].
- c. Summarize results:

This is not as easy as it sounds. Each of the six trials was done under different conditions, experts will argue vehemently whether the conditions are “slightly different” or “extremely different.” The lumpers say that there are 6 trials of **thrombolytics**, 5 negative and 1 positive and will conclude that there is no evidence supporting thrombolysis. The splitters will argue that there is only 1 **trial** of **tPA** given within 3 hours, and that this trial is positive. There is no non-experimental way of resolving this conflict. Previous ACEP Scientific Assemblies have put the issue to debate, though mud wrestling might have been more entertaining.

**\* Evidence suggests that:**

- i. **Streptokinase does not work**
- ii. **The NINDS trial using tPA produced a net benefit in mortality and functional status at 1 year. This has yet to be replicated. Taken in isolation, this trial supports the efficacy of tPA for ischemic stroke within 3 hours of onset. Despite an increase in early fatal**



hemorrhage, more patients in the tPA limb of the trial were alive at each endpoint (28% vs. 24% at one year), and their **neurologic** status was better (50% favorable outcome versus 37% favorable outcome at one year). According to this trial the number needed to treat (NNT -the number of patients that must be treated to help one patient) is about 7.

- iii. Evidence from the **PROACT II** trial of intraarterial recombinant **pro-urokinase** (Stroke 1998, 29,p.4-11) suggests that there is biological activity for this agent, offering collateral evidence that thrombolysis works in some patients.

Other references.

Wyer PC, et al. Recombinant Tissue **Plasminogen** Activator: In My Community Hospital ED, Will Early Administration of rt-PA to Patients With the Initial Diagnosis of Acute Ischemic Stroke Reduce Mortality and Disability? Ann **Emerg Med**, 1997 Nov 30(5): 629-638. Provides a succinct review of the evidence.

### 3. Issues of effectiveness

- a. The patient must be having a stroke

#### Evidence

Libman RB, et al. Conditions that mimic stroke in the Emergency Department. Implications for acute stroke trials. Arch **Neurol** 1995;52: 1119-22. Retrospective review of 411 consecutive patients diagnosed initially as stroke. 19% were deemed to have stroke mimickers including: **post-ictal** states, infections, tumors, and toxic/metabolic disturbances.

Kothari RU, et al. Emergency physicians. Accuracy **in** the diagnosis of **stroke**. Stroke. 1995 Dec;26(12):2238-41. EP diagnosis was compared with **final** CT-assisted diagnosis in 446 patients presenting **with** symptoms consistent **with** acute stroke. **EPs** identified 100% of hemorrhagic strokes and 96% of ischemic strokes, while incorrectly diagnosing stroke on 19 (4%) of patients. False + diagnoses included: seizure, complicated migraine, peripheral **neuropathy** and psychogenic paralysis.

Ferro J.M., et al. Diagnosis of **Stroke** by the **Nonneurologist**. A Validation Study. Stroke. 1998 June;29: 1106-1 109. Stroke diagnoses made by general practitioners (on 52 patients) and emergency service physicians (on 186 patients) **were** validated. 9% of GP and EPS cases had a **non-cerebrovascular** diagnosis. The conditions most frequently misdiagnosed as stroke were: cerebral tumor, 3; subdural hematoma, 1; seizure, 1; benign paroxysmal postural vertigo, 1; peripheral facial palsy, 2; psychiatric, 6; and **other** medical disorders, 7.

Gomes M da M, et al Emergency physician's diagnosis of stroke subtype. An accuracy study. Arq **Neuropsiquiatr**. 1998 Sep;56(3B):523-7. Both physician gestalt and formalized rules failed to differentiate hemorrhage from infarction on CT in stroke patients.

#### \*Evidence suggests that:

- i. **Misdiagnosis (calling a mimic a stroke) occurs in 4-19% of cases. This number decreases when mimics with abnormal CT scans are culled out. The history and physical must be sufficiently specific to ensure**

that Patients with conditions that do not declare themselves on CT (e.g. Todd's paralysis s/p seizure) are not inadvertently given thrombolytic agents. There is evidence that such cases may occasionally slip through the clinical screen.

- ii. Emergency physicians usually can make an accurate diagnosis of stroke though they cannot reliably differentiate ischemic and hemorrhagic stroke on clinical grounds.

b. The CT scan must be read correctly

Evidence regarding hemorrhage

Schriger DL, Kalafut M, Starkman S, Krueger M, Saver IL: Cranial computed tomography interpretation in acute stroke: physician accuracy in determining eligibility for thrombolytic therapy. JAMA, 1998 Apr 22-29, 279(16):1293-7.

Context: Intracranial hemorrhage must be excluded prior to thrombolytic therapy in acute stroke.

Study objective: Are physicians sufficiently skilled in interpreting cranial CT scans to identify appropriate candidates for thrombolytic therapy?

Design, Subjects & Setting: Administration of a randomly selected, randomly ordered series of CTs to a convenience sample of 38 emergency physician, 29 neurologist, and 36 general radiologist volunteers in their offices and at regional meetings.

Intervention: Presentation of 15 scans from a pool of 54 including: 17 with intracerebral hemorrhage, 19 with acute infarction, 4 with intracerebral calcifications (impostor for hemorrhage), 4 with old infarction (impostor for acute infarct), and 10 normals. For each CT the physician answered the question: "based solely on scan findings, could thrombolytics be administered to this patient: a) yes, b) no, because of hemorrhage, or c) no, because of signs of acute infarction."

Results: Physician scores ranged from 33% to 100% correct. 77% (95% CI 74%-80%) of all readings were Correct. Sensitivity for hemorrhage was 82% (95% CI 78%-85%), 52% of radiologists, 40% of neurologists, and 17% of emergency physicians achieved 100% sensitivity for hemorrhage. Overall percent correct by scan category was: "easy" bleed - 94%, "difficult" bleed - 71%, "easy" acute infarct - 91%, "intermediate" acute infarct - 69%, "difficult" acute infarct - 40%, impostor (calcification) - 75%, impostor (old infarct) - 56%, and normal - 87%.

Conclusions: Physicians did not uniformly achieve a level of sensitivity for intracerebral hemorrhage sufficient to permit safe selection of candidates for thrombolytic therapy.

Evidence regarding signs of  $> 1/3$  MCA infarction

von Kummer R, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. Radiology. 1997 Nov;205:327-333. A reanalysis of the ECASS data designed to identify the radiologically-defined subset of patients who benefit from IV thrombolysis. These 3 world-expert neuroradiologists were blinded to the clinical information, but no guarantee to blinding to the follow-up CT scans [likely biases the readings and confounds the results]. Three separate signs of major MCA ( $>1/3$ ) infarction were assessed and interrater agreement was 0.34-0.36 [kappa ranges from -1 to +1 with 0 signifying chance agreement]!

Kalafut, et al. [submitted] Reanalyzed the results of the emergency medicine, neurology, and general radiology physicians interpretations of scans (from Schriger, et al. JAMA 1998;279:1293-1297). Correct interpretation of  $>1/3$  MCA stroke was 61% for emergency physicians, 89% for neurologists, and 88% for general radiologists. 3 neuroradiologists, blinded to clinical information and follow-up scans, evaluated each scan for signs of  $>1/3$  MCA territory infarct, with unanimous agreement in only 67% of cases. For smaller strokes ( $<1/3$  MCA), all 3 unanimously agreed on only 4 of 12 (33%) scans, and for "normal" scans unanimous agreement was 6/11 (55%).

**\*Evidence suggests that:**

- i. **identification of hemorrhage is not an easy task and that special training is required. The content and effectiveness of that training is yet to be defined.**
  - ii. **The art of identifying the various signs of infarction on plain CT remains somewhere between Ouiji board and Rorschach. New imaging modalities could simplify this process.**
- c. Time since symptom onset must be correctly ascertained

Evidence – no specific evidence regarding the accuracy of times

There is some evidence regarding patient and bystander estimates of the duration of events (cardiac arrest, seizures) that suggests that time estimates can be wildly inaccurate. However, even if patients who were truly more than 3 hours were enrolled in NINDS, the result still holds,

**\*\* Overall the evidence for effectiveness suggests:**

- i. **There is no trial demonstrating effectiveness. Abstracts of large case series are appearing but most are not yet published.**

Chiu D, et al. Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke. Feasibility Safety, and Efficacy in the First Year of Clinical Practice. Stroke, 1998 Jan;29( 1): 1X-22. Of the patients hospitalized with ischemic stroke, 6% received t-PA at the university hospital and 1.1% at the community hospitals. The rates of total , symptomatic, and fatal intracerebral hemorrhage were 10%, 7%, and 3%.

- ii. **Much like carotid endarterectomy, results from community administered IV tPA will likely vary based on the quality of the team providing the care.**
- iii. **We await an RCT done in the community with community doctors providing care (preferred), or a comprehensive case-series demonstrating the reproducibility of the NINDS results.**

**4. Issues of Efficiency**

- a. Patients must know they are having a stroke and present for care

Evidence – know they are having a stroke

Pancioli AM, et al. Public perception of stroke warning signs and knowledge of potential risk factors. JAMA. 1998 Apr 22-29;279(16):1288-92. The authors surveyed a randomly selected population of 2642 subjects in and around Cincinnati, OH regarding their knowledge of stroke symptoms. Only 57% could list one of the 5 common symptoms of stroke onset. 28% could list 2, and 8% could list 3.

Kothari R, et al. Patients' awareness of stroke signs, symptoms, and risk factors. *Stroke*. 1997 Oct;28(10):1871-5. Over 40% of 163 patients admitted to the ED with stroke symptoms could not name one symptom of acute stroke. Patients over 65 were less likely to know the symptoms.

Williams LS, et al. Stroke patients' knowledge of stroke. Influence on time to presentation. *Stroke*. 1997 May;28(5):912-5. Roughly ¼ of patients presenting with acute stroke had figured out that they were having a stroke when they presented. 38% of patients claimed to know the symptoms of stroke.

**\* Evidence suggests that:**

- i. **The majority of those at risk have only fair knowledge of the signs and symptoms of acute stroke.**
- ii. **The presence of another person often aids in the early identification of stroke**

Evidence – patients promptly activate the health care system

Smith MA, et al. Delayed hospital arrival for acute stroke: the Minnesota Stroke Survey. *Ann Intern Med*. 1998 Aug 1;129(3):190-6. Roughly 1/3 of patients presented within 3 hours. Those with prior stroke, MI or more symptoms tended to present sooner.

Azzimondi G, et al. Variables associated with hospital arrival time after stroke: effect of delay on the clinical efficiency of early treatment. *Stroke*. 1997 Mar;28(3):537-42. Hemiparesis, altered mental status, being awake when onset occurred, predict earlier presentation.

Barsan WG, et al. Time of hospital presentation in patients with acute stroke. *Arch Intern Med*. 1993 Nov 22;153(22):2558-61. 2099 subjects with times available for 1159.39% arrived within 90 min, 59% within 3 hours. Calling 911 associated with faster times [but is likely confounded by severity], longer times when stroke begins at night, longer at home versus in public place [also likely confounded].

Kothari R, et al. Acute stroke: delays to presentation and emergency department evaluation. *Ann Emerg Med*. 1999 Jan;33(1):3-8. Survey of times of 151 stroke patients of whom 119 had a known time of onset. 30% arrived within 3 hours. Early presentation was associated with white race, use of EMS, and being with someone who made the decision (as opposed to the patient making it themselves).

Jorgensen HS, et al. Factors delaying hospital admission in acute stroke: the Copenhagen Stroke Study. *Neurology*. 1996 Aug;47(2):383-7. 1,198 prospectively identified stroke patients of whom 25% presented with >3.5 hours. Presence of social network and increased symptom severity were associated with early presentation as did previous stroke/TIA.

Rosamond WD, et al. Rapid response to stroke symptoms: the Delay in Accessing Stroke Healthcare (DASH) study. *Acad Emerg Med*. 1998 Jan;5(1):45-51. Another predictor study showing that use of EMS is associated with earlier presentation. Of course, use of EMS is no doubt related to symptom severity.

Wester P, et al. Factors Associated With Delayed Admission to Hospital and In-Hospital Delays in Acute Stroke and TIA. A Prospective, Multicenter Study. *Stroke*. 1999 Jan;30:40-48. A model created in this Swedish population explained 45% of the variance in time to presentation and suggested that risk factors for delayed presentation include: patients with a brain infarct, gradual onset, mild neurological symptoms, patients who were alone and did not contact anybody when symptoms occurred, patients who lived in a densely populated area, those who did not use ambulance transportation, and those who visited a primary care site.

**\*Evidence suggests that:**

- i. Those with severe symptoms are more likely to present sooner (but they are also at higher risk of having a hemorrhagic stroke).**
- ii. Having someone else notice that you are having a stroke is the best way to get care quickly.**
- iii. There is a wide range of reported values for the number of patients who present in time to be given tPA within 3 hours. The number is likely under 30% nationwide at this time.**

- b. Patients must receive the proper advice when they contact the health care system.

Evidence — none

It is unclear to what extent educational efforts have made primary care providers aware that strokes or “Brain Attacks” as the publicity calls them are an emergency that requires immediate attention.

- c. The emergency system must provide rapid: evaluation, cranial CT, CT reading and treatment.

Evidence

The trials demonstrate that it is possible to get tPA to patients within 3 hours. Several quality improvement efforts have been reported which provide suggestions regarding how speed evaluation, imaging and therapy. At academic centers and their surrounding hospitals, the stroke team approach is a popular method.

- d. The patient must have an ischemic stroke that meets eligibility criteria for treatment.

Evidence —

Hemorrhagic stroke consistently accounts for 10-15 % of all strokes  
Other stroke mimickers may account for another 10% of those presenting with an acute neurologic deficit. (see C.3.a)

**\*\* Overall assessment of efficiency**

- i. For every 100 persons presenting with acute neurologic deficits, at most 30 will arrive in time to permit drug administration within 3 hours (meaning they arrive within 150 minutes). Of these 30, roughly 30% will have either a mimic, a hemorrhage on CT, or another contraindication, leaving at most 20 patients who are potentially eligible. The percentage of screened patients who were enrolled in the RCTs varies from 1 in 200 to 5 in 100. Using these numbers, one must evaluate 350 patients to successfully treat 1 person. (NNT of 7 x 50 [reciprocal of 2 enrolled subjects per 100 screened]).

**D. Overall outcome**

1. There is one well-done RCT [the two trials of NINDS] which shows that tPA is efficacious. There is minimal evidence establishing its effectiveness. If effectiveness equals efficacy, roughly 350 patients would require evaluation to improve one patient's outcome.
2. There exist concerns regarding the health care delivery system's ability to exclude mimics, properly interpret cranial CTs, and correctly determine the time of onset. If these actions are not done properly effectiveness numbers will be lower than the efficacy data.
3. Patients will hemorrhage and die acutely from thrombolytic therapy; many of these patients would have done poorly had the drug been withheld. An occasional patient will have a poor outcome because of misadministration of tPA. Society and physicians will have to weigh their distaste for such an event against the benefit provided to those for whom the drug works.
4. Thrombolytics unquestionably have biological activity in stroke. The current agents may be harbingers of future drugs and techniques that are safer and more effective.



## Characteristics of Thrombolysis in Stroke Studies

			Sites			Timing	Age	Clinical	Clinical	
ECASS (DBRCT)	10/95	JAMA	75	14 European Countries	rtPA (1.1 mg/kg) placebo	< 6 hrs	18-80	mod-severe hemispheric stroke	↓LOC, preexisting neurologic, tPA CI	CT
MAST-I (RCT)	12/95	Lancet	70	Mostly Italy	streptokinase 1.5 mill u ASA 300 qd x 10 d Both Neither	< 6 hrs	adults	stroke	severe coma, rapid recovery, SK/ASA CI	blood
NINDS (DBRCT)	12/95	NEJM	40-50	Across U.S.	rtPA (0.9 mg/kg) placebo	< 3 hrs	adults	deficit, BP ok	recent stroke, tPA CI, recent coum/hep	blood
MAST-E (DBRCT)	7/96	NEJM	48	England/France	streptokinase 1.5 mill u placebo	< 6 hrs	adults	mod-severe MCA stroke	rapid recovery, prev. stroke w/ sx, SK CI	blood, tumor
ASK (DBRCT)	9/96	JAMA	40	Australia	streptokinase 1.5 mill u placebo	< 4 hrs	18-85	acute stroke	mild, coum/hep, SK CI, prev. stroke	blood, tumour
ECASS-II (DBRCT)	10/98	Lancet	108	14 European Countries, Australia, and New Zealand	rtPA (0.9 mg/kg) placebo	< 3 hrs & < 6 hrs	18-80	Mod-severe hemispheric	coma or stupor, minor stroke sx, sig. HTN, rtPA CI	blood, signs of major infarction

CI = contraindications

ECASS - Hacke, W., et al, JAMA 274(13):1017, October 4, 1995

MAST-I - Italy (MAST-I) Group, Lancet, 346:1509, December 9, 1995

NINDS - The National Institute of Neurologic Disorders and Stroke rt-PA Stroke Study Group, NEJM 333(24):1581, December 14, 1995

NINDS - The National Institute of Neurologic Disorders and Stroke rt-PA Stroke Study Group, NEJM 340(23):1781, June 10, 1999

MAST-E - Europe Study Group, NEJM 335(3):145, July 18, 1996

ASK - Donnan, G., et al, for the Australian Streptokinase Trial Study Group, JAMA 276(12):961, September 25, 1996

ECASS-II - Hacke W, et al., Lancet. 1998 Oct 17;352(9136):1245-51.



## Results of Thrombolysis in Stroke Studies

Trial	Drugs	N (altered N)	Primary measures		Main Results ITT [C]	Safety Results		Conclusions
			Scale(s)	When		Sx hemorrhage	Mortality	
ECASS (DBRCT)	rtPA (1.1 mg/kg)	313 (247)	Barthel	90d	No difference	134 (42.8%)	69 (22.4%)	"Cannot be recommended"
	placebo	307 (264)	Rankin		[Rankin sl better in rtPA]	113 (36.8%)	48 (15.8%)	
MAST-I (RCT)	streptokinase 1.5 mill u	157	Modified Rankin	6 mo	Fatality + disability	10 (6%)	44 (28%)	"Increased early death"
	ASA 300 qd x 10 d	153			SK = 63%	3 (2%)	30 (20%)	"Marginal reduction of severe disability at 6 months"
	Both	156			PLAC = 65%	15 (10%)	68 (44%)	
	Neither	156			OR 0.9 (0.7-1.3)	1 (0.6%)	45 (29%)	
NINDS (DBRCT)	rtPA (0.9 mg/kg)	312	Barthel Rankin	24 h & 90 d	Part I (24 hr outcome) = no difference	20 (6%) – 36 h	54 (17%) – 90 d	"Despite increased hemorrhage... improved outcome at 3 months and at 12 months"
			Glasgow NIHSS	90 d & 12 mo	Part II (90 d) rtPA better OR 1.7 (1.2-2.6)	25 (8%) – 12 mo	75 (24%) – 12 mo	
	placebo	312			Part III (12 mo) rtPA better OR 1.7 (1.2-2.3)	2 (0.6%) – 36 h 5 (1.6%) – 12 mo	64 (21%) – 90 d 87 (28%) – 12 mo	
MAST-E (DBRCT)	streptokinase 1.5 mill u	156	Binary (death or Rankin >2)	6 mo	TRIAL STOPPED	33 (21%)	53 (34%) [10 day]	"Routine use of SK cannot be recommended"
	placebo	154			No difference in overall scale	4 (2.6%)	73 (45%) [6 mo] 28 (18%) [10 day] 59 (38%) [6 mo]	
ASK (DBRCT)	streptokinase 1.5 mill u	174	Binary (death or Barthel <60)	3 mo	TRIAL STOPPED	21 (12.6%)	63 (38%)	"SK increased 3 mo morbidity and mortality" "Timing of therapy is critical"
	placebo	166			no difference – trend to streptokinase worse especially when > 3 hrs.	4 (2.4%)	34 (21%)	
ECASS-II (DBRCT)	rtPA (0.9 mg/kg)	409	Rankin	90d up to 104d	rtPA 3.7% better for independence (OR 1.17 (0.9-1.6))	48 (12%)	43 (11%)	".. do not confirm a statistical benefit. However, trend +"
	placebo	391				12 (3%)	42 (11%)	

Rankin = Modified Rankin, a seven point ADL scale

Rankin = Modified Rankin, a seven point ADL scale

Sx hemorrhage = symptomatic hemorrhage

ITT - Intention to treat - everyone enrolled is counted in their assigned group

C - Completer analysis - only those who followed the entire protocol correctly are counted