IV tPA: To treat or Not to Treat?

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Today's Final Jeopardy Question:

What is 77 mg?

Key Points

tPA for ischemic stroke is:

- Safe and effective up to 4.5 hrs
- Most patients treated do not benefit

- Better reperfusion strategies needed
- Better patient selection critical; especially in later time windows

Clinical Trial Analysis

- Primary vs. secondary endpoints
- Positive subgroups in negative trials
- Negative subgroups in positive trials
- Imbalances in baseline characteristics

New England Journal, 1995

NINDS tPA Stroke Trial Primary Endpoints

Part 1 (N=290):

Early Improvement > 4 or full recovery on NIHSS at 24 hrs (%)

Part 2 (N=333):

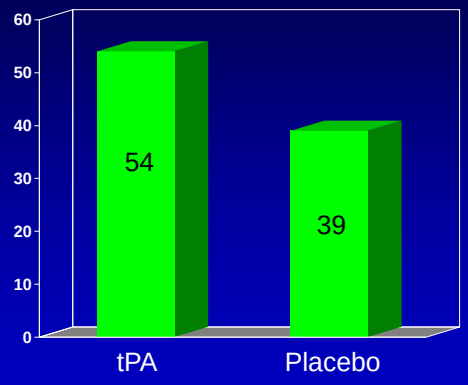
Recover with minimal or no deficit at 90 days

Global test

			OR	RR	
No. of patients	168	165			
Global test	—	—	1.7 (1.2–2.6)	—	0.008
Barthel index	50	38	1.6 (1.1–2.5)	1.3 (1.0–1.7)	0.026
Modified Rankin scale	39	26	1.7 (1.1–2.6)	1.5 (1.1–2.0)	0.019
Glasgow outcome scale	44	32	1.6 (1.1–2.5)	1.4 (1.0–1.8)	0.025
NIHSS	31	20	1.7 (1.0–2.8)	1.5 (1.0–2.2)	0.033

New England Journal, 1995

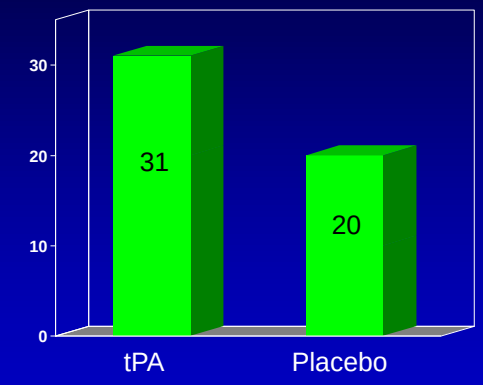
NINDS tPA Stroke Trial: Spin Doctors



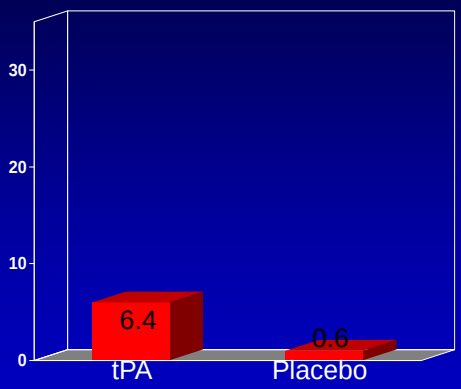
Barthel Index: Excellent Recovery (95-10) (%)

New England Journal, 1995

NINDS tPA Stroke Trial: Spin Doctors



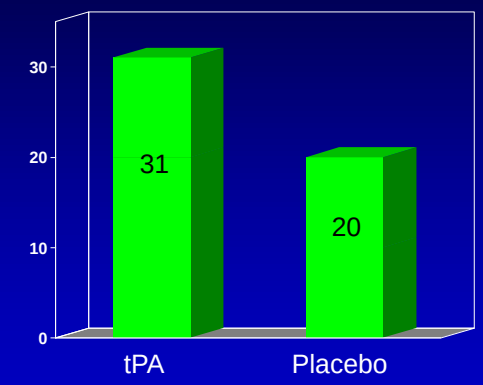
NIHSS Excellent Recovery (0-1) (%)



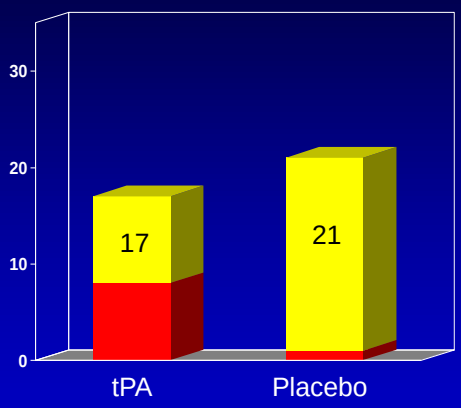
ICH Rate (%)

New England Journal, 1995

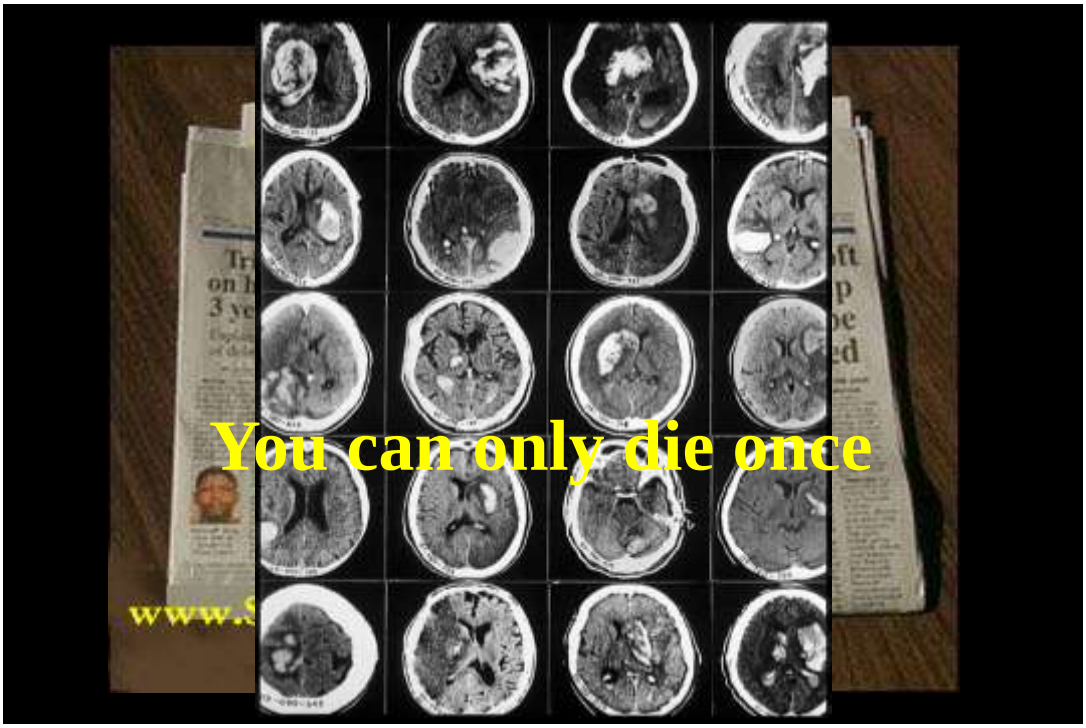
NINDS tPA Stroke Trial



NIHSS Excellent Recovery (0-1) (%)



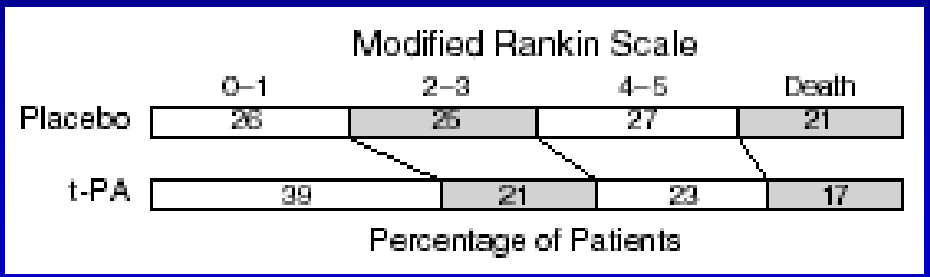
Total Death Rate (%)



New England Journal, 1995

NINDS tPA Stroke Trial: Bottom Line

Increases in Good Outcomes Reductions in Bad Outcomes



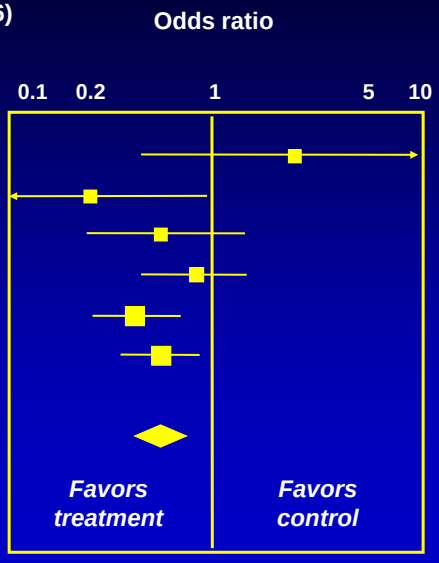
Large Randomized Trials of IV t-PA for Treatment of Acute Stroke

Study	N	Dose	Time Window
ECASS I	650	1.1	0 – 6
NINDS	624	0.9	0 – 3
ECASS II	800	0.9	0 – 6
ATLANTIS A	142	0.9	0 – 6
ATLANTIS B	619	0.9	3 – 5

Trials of IV t-PA: 0-3 Hr Time Window

Study	Number showing poor outcome (mRS 3-6) / total number of patients: t-PA	Control
Atlantis A	8/10	7/12
Atlantis B	4/13	17/26
ECASS 1	30/49	26/36
ECASS 2	47/81	48/77
NINDS Trial 1	76/144	107/147
NINDS Trial 2	103/168	122/165
Total	266/465	329/465

Odds Ratio 0.56 (0.42-0.73)
P=0.00002



Saver J, et al *BMJ* 2002:324:727-729

Better Outcome With Early Stroke Treatment: A Pooled Analysis of the ATLANTIS, ECASS, and NINDS rtPA Stroke Trials

The ATLANTIS, ECASS, and NINDS Study Group Investigators

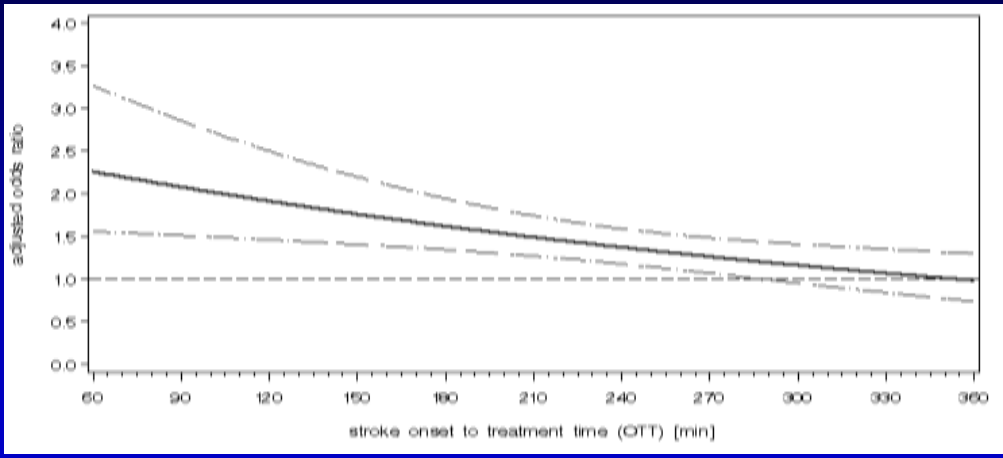
Lancet 2004

Results

- 2776 patients
- Over 300 hospitals
- 18 countries
- Median age 68 years
- Median baseline NIHSSS 12

Modified Rankin 0-1 at Day 90

Adjusted* odds ratio (95% CI) by stroke onset to treatment time, (N=2776)



*Adjusted for baseline imbalances in age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension and interaction between age and baseline NIHSS measurement.

Results

Adjusted Odds Ratios for Favorable Outcome*

Time	Odds Ratio	95% (CI)
0-90	2.8	1.8 - 4.5
91-180	1.5	1.1 - 2.1
181-270	1.4	1.1 - 1.9
271-360	1.2	0.9 - 1.5

*Rankin (0–1), Barthel (95–100), and NIHSS (0–1). Odds ratios calculated from global statistic

ECASS 3

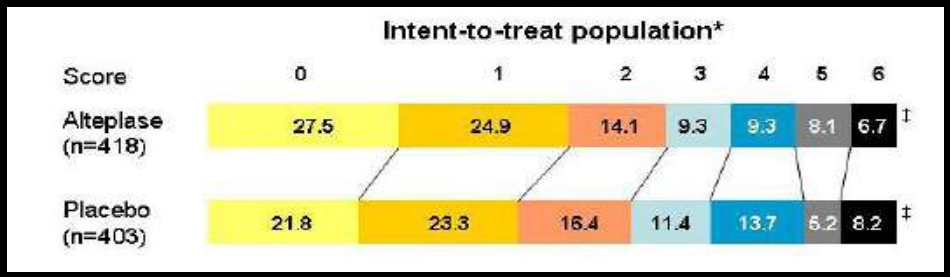
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2008 VOL. 359 NO. 13

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghri, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*

ECASS 3 Results (3-4.5 hr window)



Good outcome (mRS 0-1): 52% with tPA vs 45% with placebo; p= 0.04

SICH: ECASS definition (≥ 4 pts NIHSS): tPA 2.4%, placebo 0.2%

SICH: NINDS definition (any neuro decline): tPA 7.9%, placebo 3.5%

Time dependent response to treatment with i.v. alteplase for stroke: An updated pooled analysis of ECASS, ATLANTIS, NINDS and EPITHET rt-PA stroke trials

KR Lees, E Bluhmki, R von Kummer, T Brott, D Toni, J Grotta, G Albers, M Kaste, J Marler, S Hamilton, B Tilley, SM Davis, GA Donnan, W Hacke for the *ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group Investigators*

Lancet 2010, 375: 1695–1703

Methods

- Individual data from eight trials with all necessary variables (mRS, NIHSS, Barthel Index, PH2) :
  - NINDS (part 1, part 2); ATLANTIS (A, B); ECASS (-1, -2, -3); EPITHET
- Primary endpoints - interaction with onset to treatment time (OTT) for :
  - favorable outcome at 90 days - modified Rankin 0,1
  - global test at 90 days - mRS 0-1; Barthel 95-100; NIHSS 0-1
  - mortality at 90 days
  - parenchymal hemorrhage type 2 (PH2) - adjudicated by common rule
- Secondary analyses - effect within each time epoch (0-90, 91-180, 181-270, 271-360 minutes)
  - odds ratio and 95% CI for each primary outcome measure
  - distribution of mRS

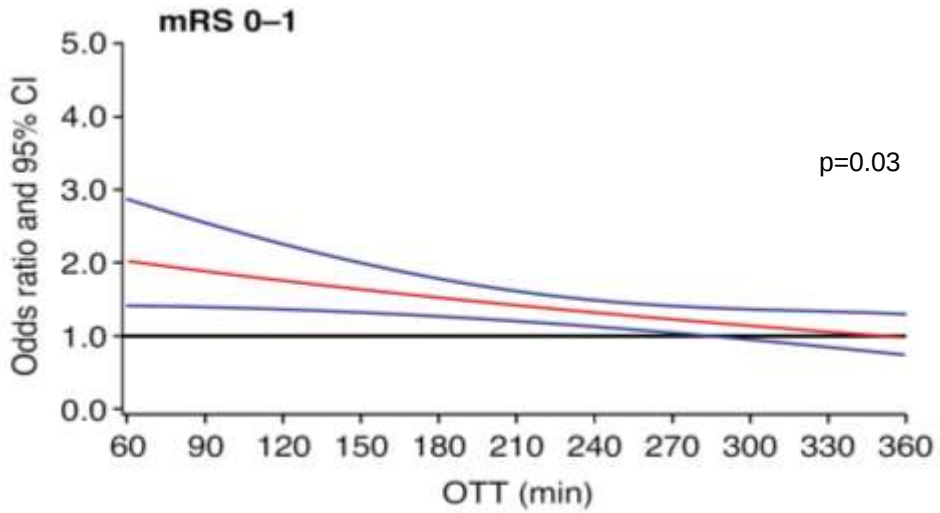
Demography of patients in the pooled analysis

		Placebo 1820		Alteplase 1850	
Age (y)	mean, SD	66	11	66	12
NIHSS	median, IQR	11	7-16	11	7-16
0-90min		15	10-19	15	10-20
91-180min		13	9-19	11	7-18
181-270min		11	7-16	10	7-15
271-360min		10	7-15	10	7-16
OTT (min)	mean, SD	232	73	233	72
SBP (mmHg)	mean, SD	152	21	153	21
DBP (mmHg)	mean, SD	84	14	84	13
Weight (kg)	mean, SD	77	16	76	16
Prior diabetes	%	18		19	
Prior stroke	%	15		14	
Prior AF	%	19		19	
Prior hypertension	%	57		57	
Prior aspirin	%	26		26	

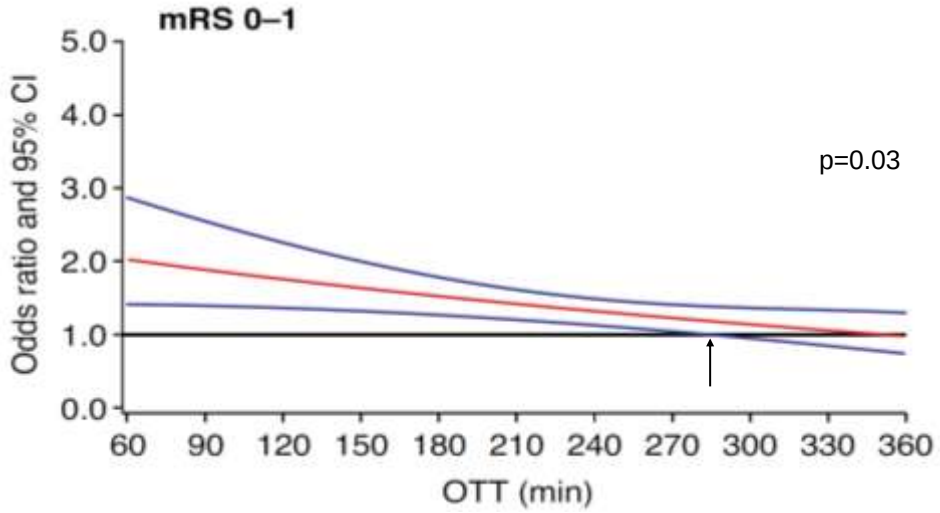
Groups are well matched on all relevant variables

Analyses adjusted for OTT, age, NIHSS, blood pressure, prior stroke, interaction of age and NIHSS

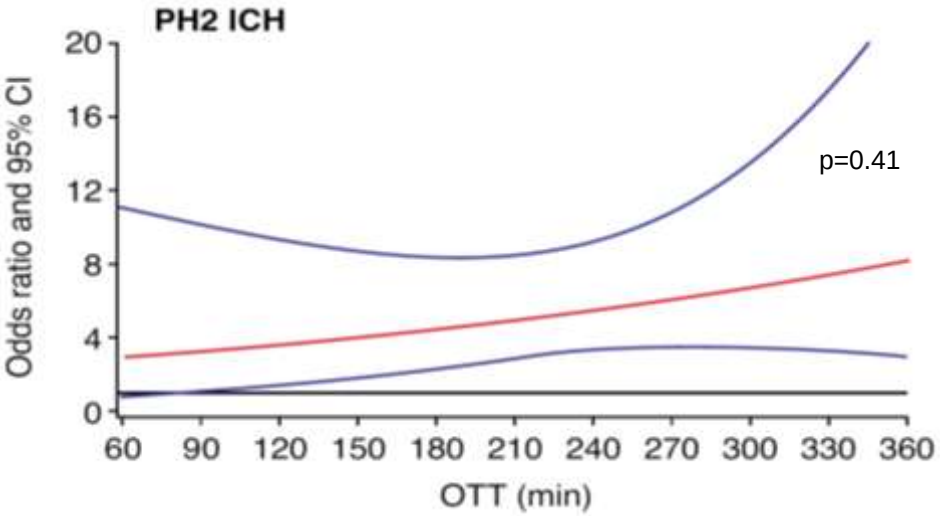
Excellent outcome (mRS 0-1), n=3530



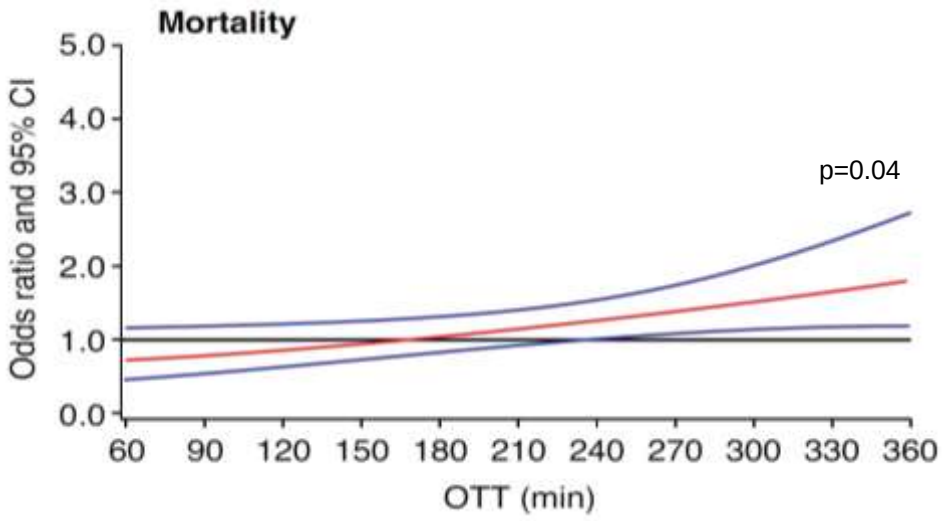
Excellent outcome (mRS 0-1), n=3530



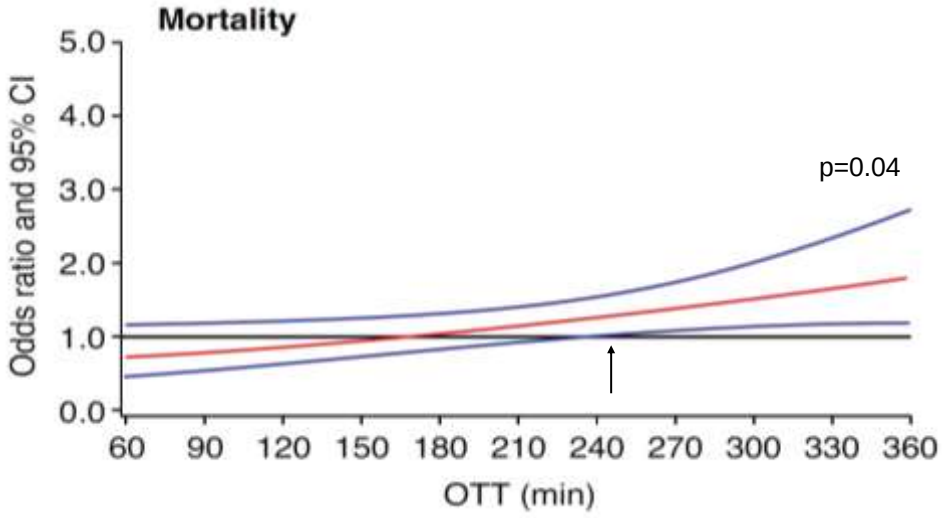
Symptomatic hemorrhage (PH2), n=3431



Mortality, n=3530



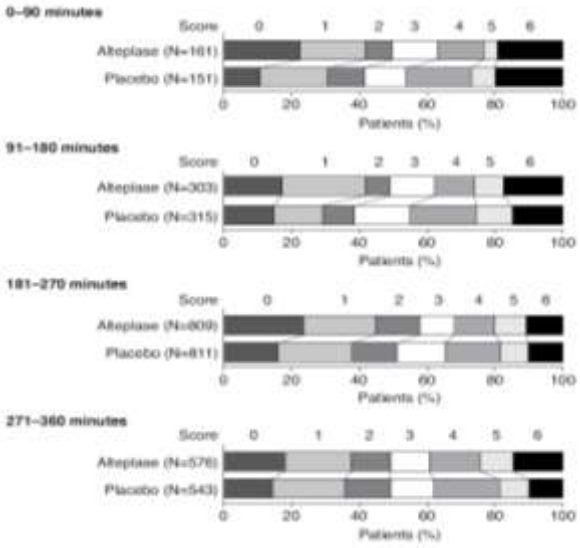
Mortality, n=3530



Odds ratios by Onset to Treatment

	Global	mRS	Mortality
0-90	2.84 1.75-4.60	2.55 1.44-4.52	0.78 0.41-1.45
91-180	1.52 1.10-2.11	1.64 1.12-2.40	1.13 0.70-1.82
181-270	1.32 1.09-1.61	1.34 1.06-1.68	1.22 0.87-1.71
271-360	1.22 0.96-1.54	1.22 0.92-1.61	1.49 1.00-2.21

Distribution of modified Rankin Scale



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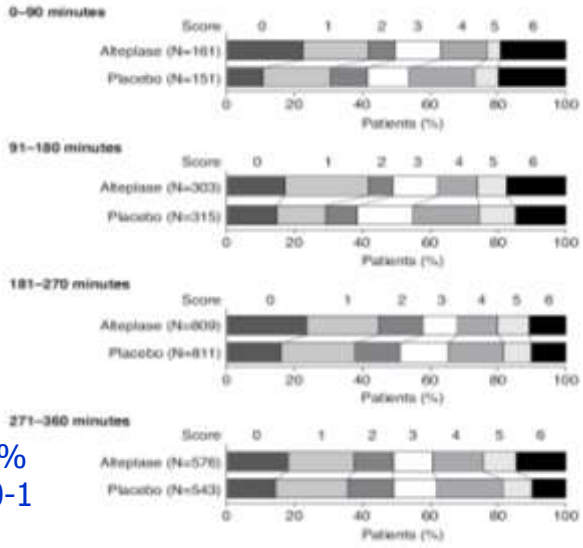

+ 1.8%
mRS 0-1

+ 4.8%
mortality

Table 2

	Modified Rankin score 0–1 at 90 days*, n/N (%)		Odds ratio (95% CI)	p value	Estimated number needed to treat† for modified Rankin score 0–1
	Alteplase, n/N (%)	Placebo, n/N (%)			
0–90 min	67/161 (41·6%)	44/151 (29·1%)	2·55 (1·44–4·52)	0·0013	4·5
91–180 min	127/303 (41·9%)	91/315 (28·9%)	1·64 (1·12–2·40)	0·0116	9·0
181–270 min	361/809 (44·6%)	306/811 (37·7%)	1·34 (1·06–1·68)	0·0135	14·1

I rest my case!