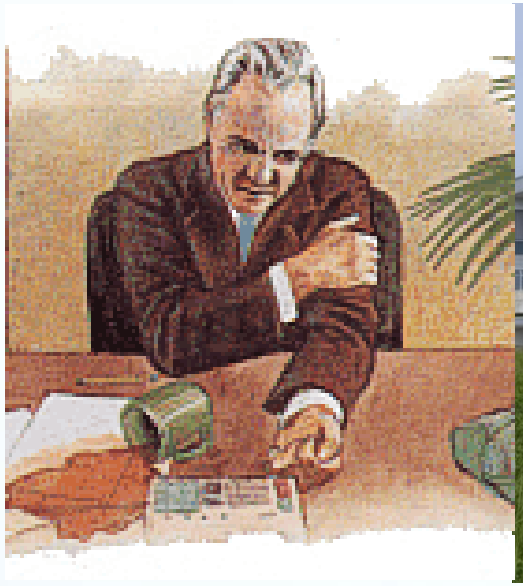
UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

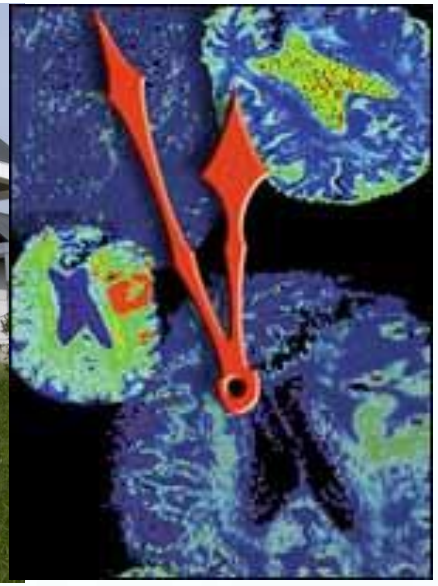
SCUOLA SUPERIORE DI NEUROLOGIA

IV° Corso: Nuovi sviluppi nel trattamento acuto dell'ictus ischemico

Genova, 16 Febbraio 2016

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Modena





Trombolisi endovenosa:

Principi, efficacia, trials registrativi

Dr. Andrea Zini
Responsabile Stroke Unit
Dipartimento di Neuroscienze
Nuovo Ospedale Civile "S.Agostino-Estense"
AUSL Modena

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ARGOMENTI

TROMBOLISI ENDOVENOSA

- PRINCIPI
- EFFICACIA
- TRIALS REGISTRATIVI

PRINCIPI

Terapia trombolitica

- Terapia volta a dissolvere trombi/emboli nelle arterie, migliorare il flusso ematico e prevenire danni a tessuti e organi
- Indicazioni:
  - IMA
  - Embolia polmonare
  - Ictus

Ricordiamoci che:

- ✓ Le arterie cerebrali non sono assimilabili alle arterie degli altri distretti corporei, incluse le coronarie

- ✓ Il cervello non è un muscolo…e tutto ciò che ne consegue

- ✓ L'eziologia dell'ictus ischemico è complessa (AT,CE,LA, IND, DIS, ecc)

MA…

- ✓ L'ictus è una patologia tempo-dipendente

LA STROKE UNIT
è la prima terapia dell'ictus

Organised inpatient (stroke unit) care for stroke (Review)

Stroke Unit Trialists' Collaboration

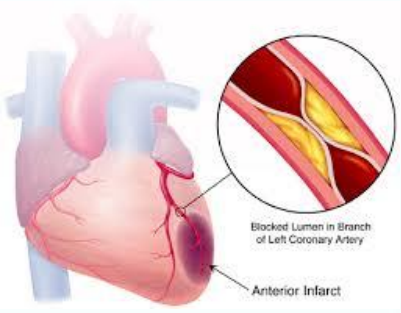
THE COCHRANE COLLABORATION®

Stroke patients who receive organised inpatient care in a Stroke Unit are more likely to be alive, independent, and living at home one year after the stroke.

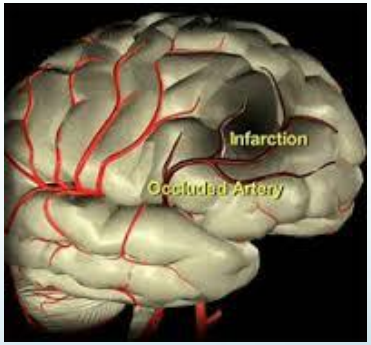
The Cochrane Library 2009, Issue 1)

Prove di efficacia

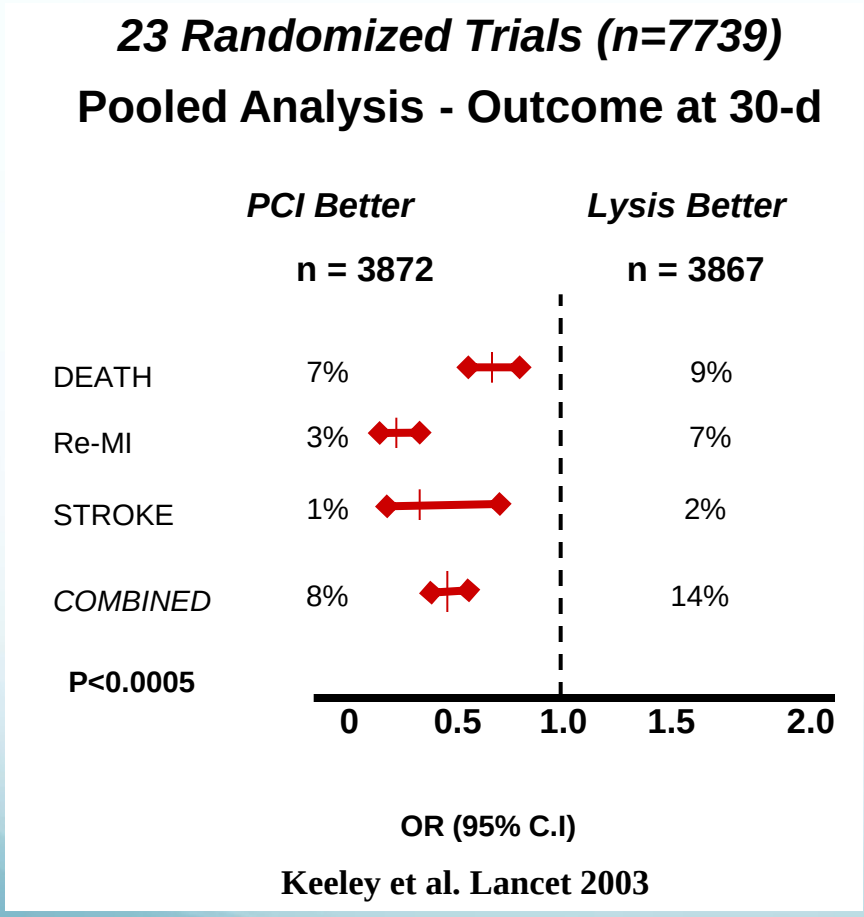
dall' IMA

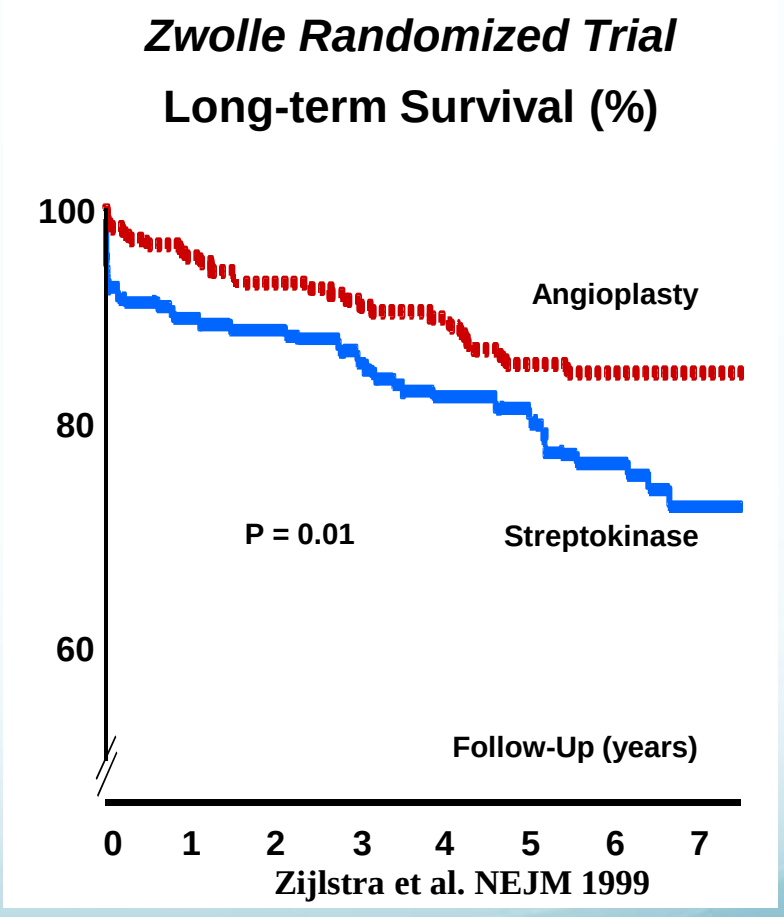


all' ICTUS

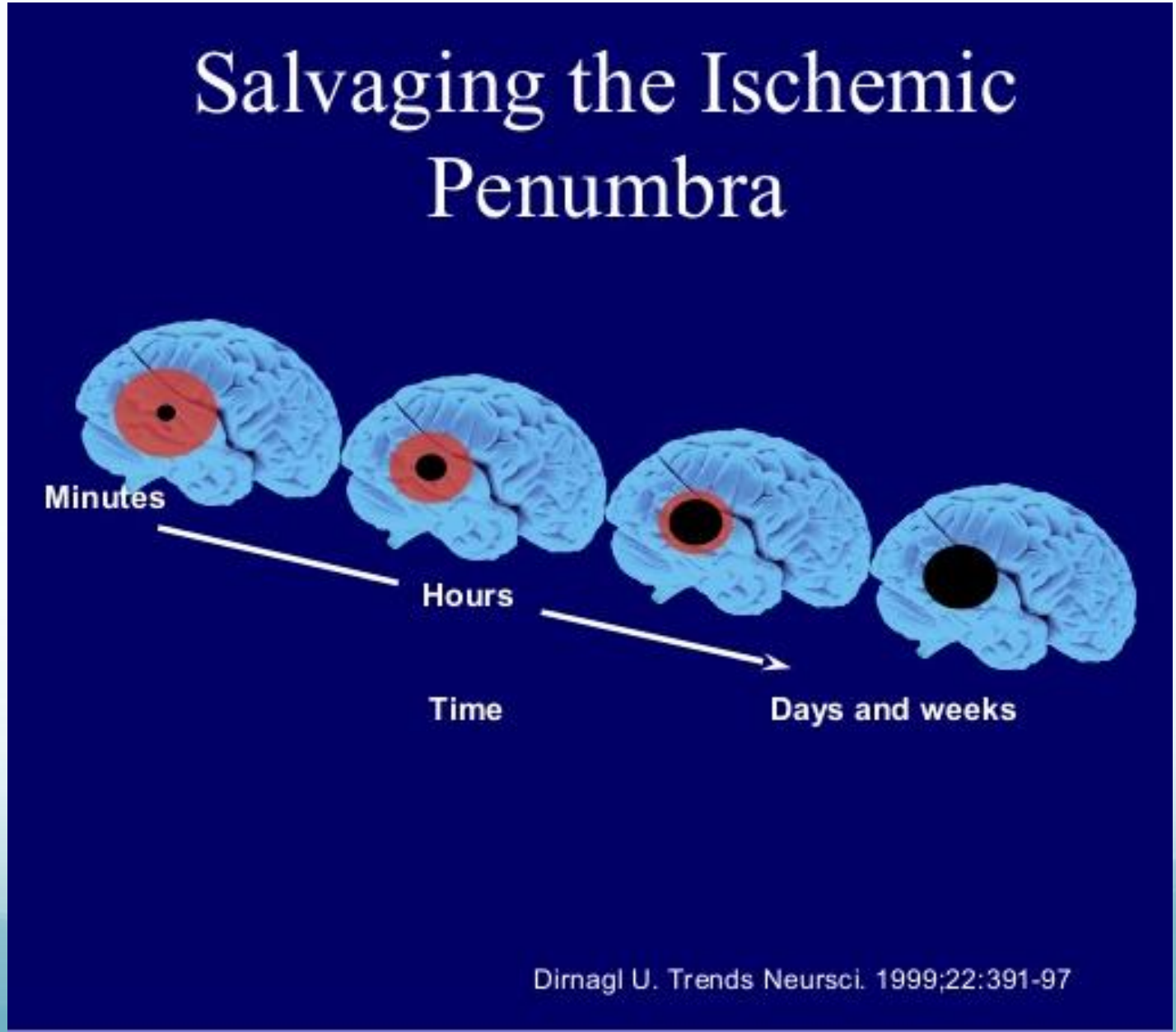


IMA: angioplastica primaria vs. trombolisi ev





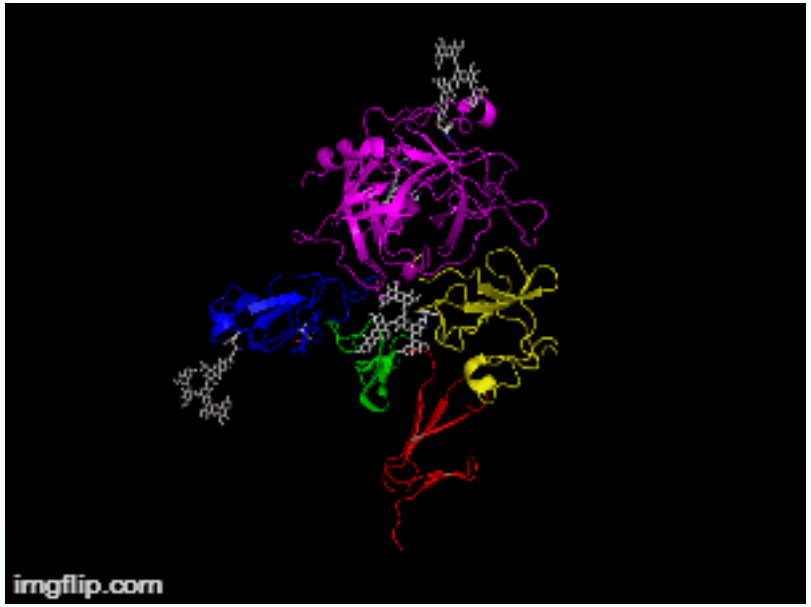
Penombra ischemica

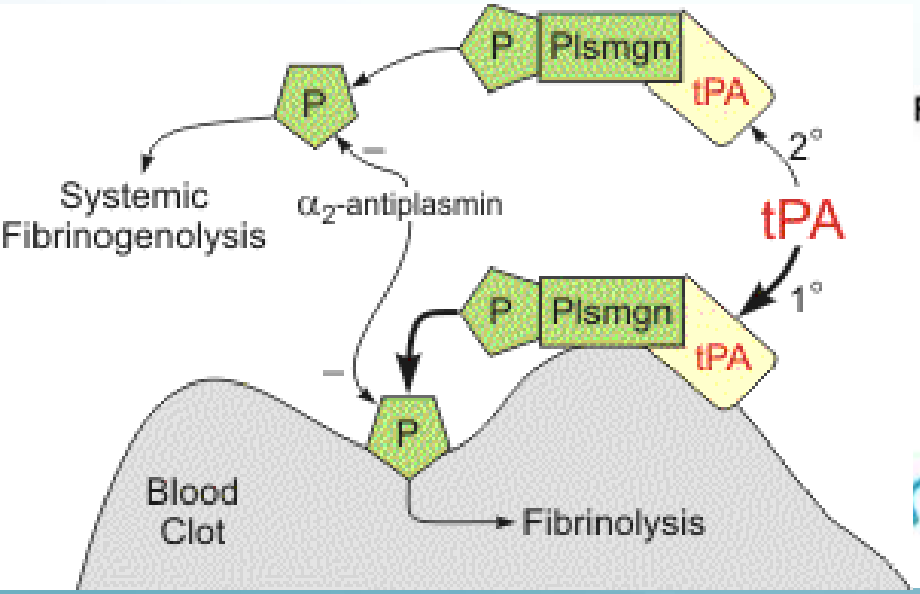


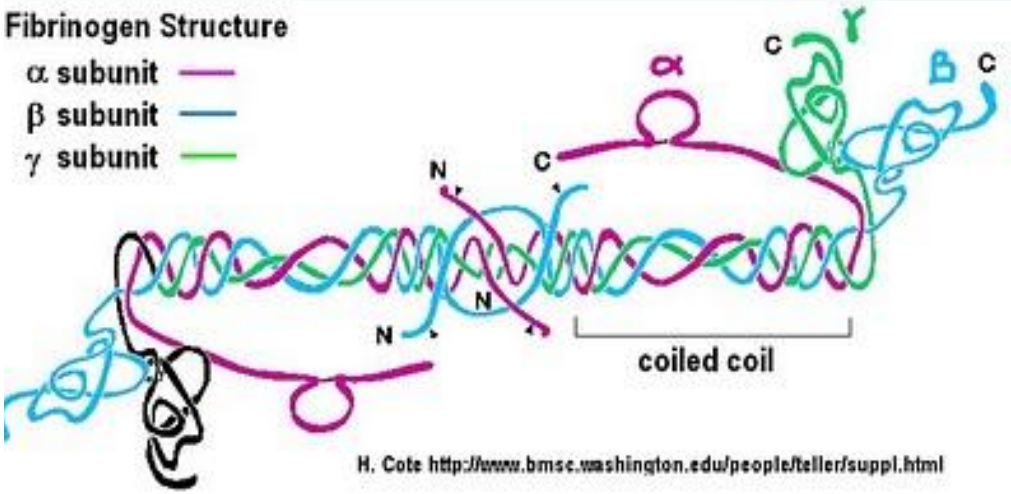
Agenti trombolitici

- Streptokinase
- Urokinase
- rt-PA (Alteplase)
- Reteplase
- TNK (tenecteplase)
- Desmoteplase
- Lanoteplase

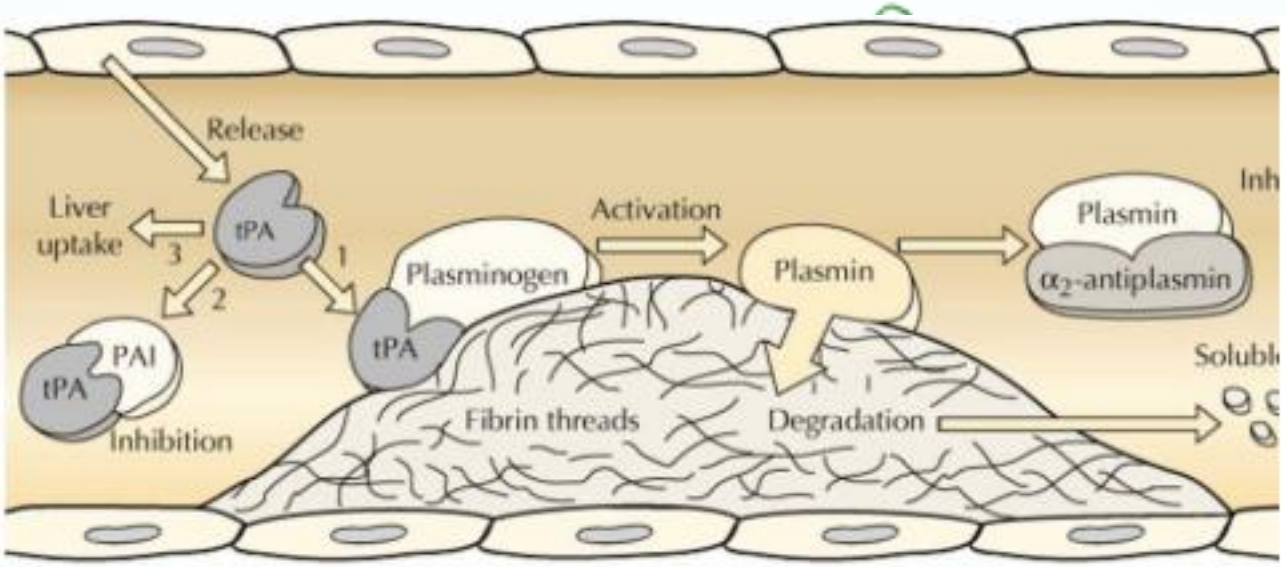
rtPA

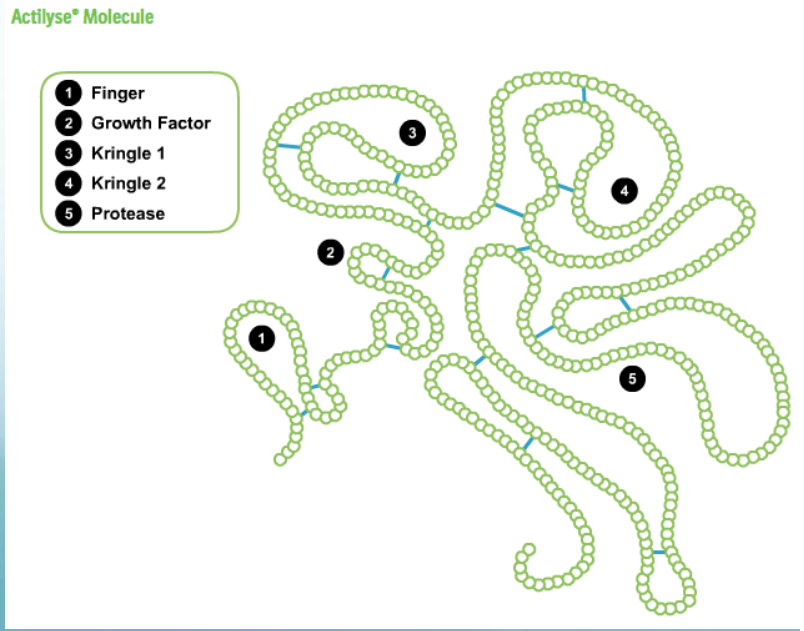

imgflip.com

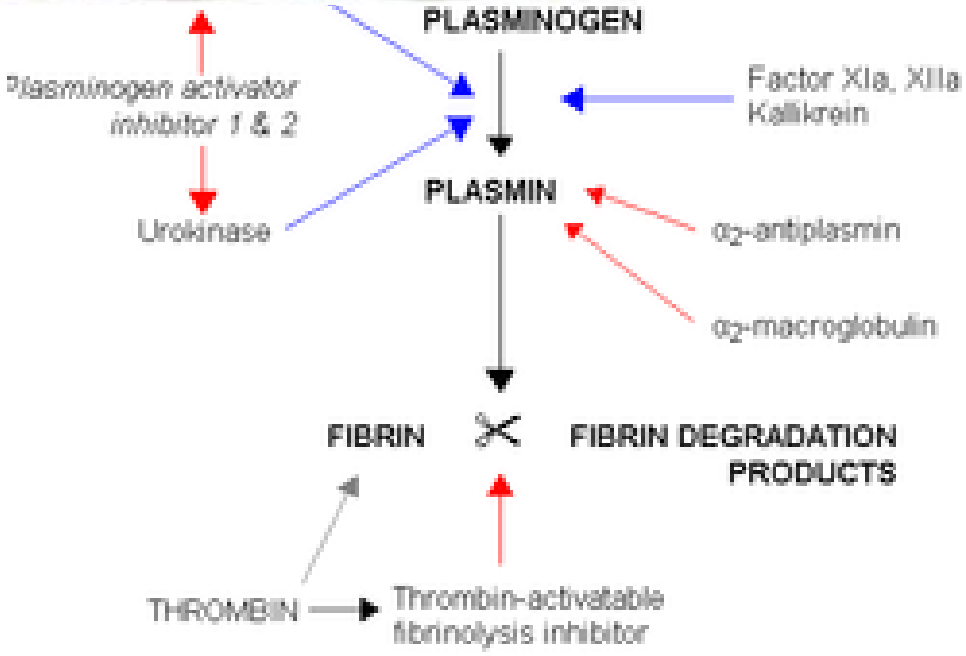

P
Plsmgn
tPA
2°
tPA
1°
Systemic
Fibrinogenolysis
α2-antiplasmin
Blood
Clot
Fibrinolysis


Fibrinogen Structure
α subunit
β subunit
γ subunit
N
C
coiled coil
H. Cote http://www.bmsc.washington.edu/people/teller/suppl.html

rtPA


Release
Liver uptake
tPA
3
2
1
PAI
tPA
Inhibition
Plasminogen
tPA
Activation
Plasmin
Plasmin
α2-antiplasmin
Fibrin threads
Degradation


Actilyse® Molecule
1 Finger
2 Growth Factor
3 Kringle 1
4 Kringle 2
5 Protease


PLASMINOGEN
Plasminogen activator inhibitor 1 & 2
Factor XIa, XIIa
Kallikrein
Urokinase
PLASMIN
α2-antiplasmin
α2-macroglobulin
FIBRIN
FIBRIN DEGRADATION PRODUCTS
THROMBIN
Thrombin-activatable fibrinolysis inhibitor

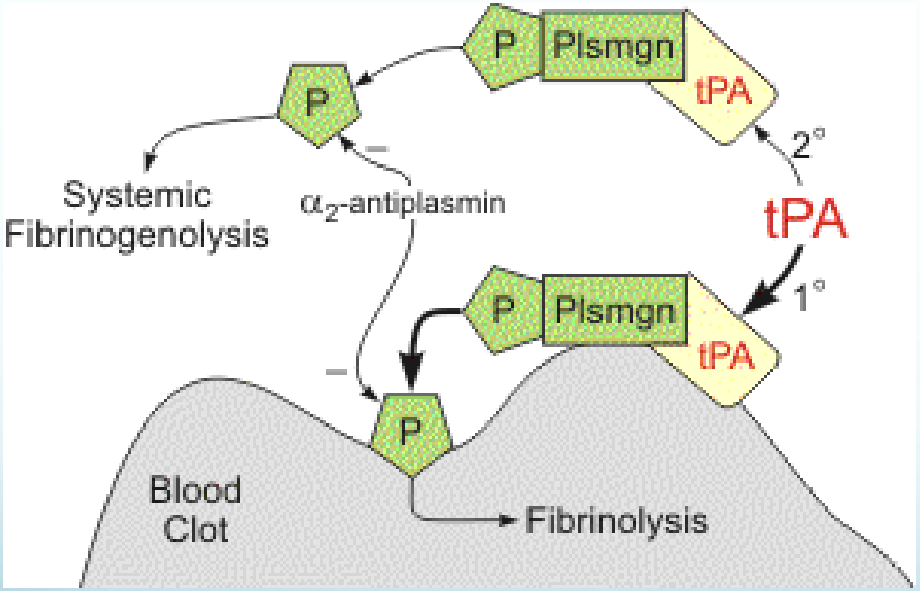
Trombolitici: selettività

Table 1. A comparison of the current thrombolytic drugs that are available in term of plasma half life, fibrin specificity and susceptibility to inhibition[57]

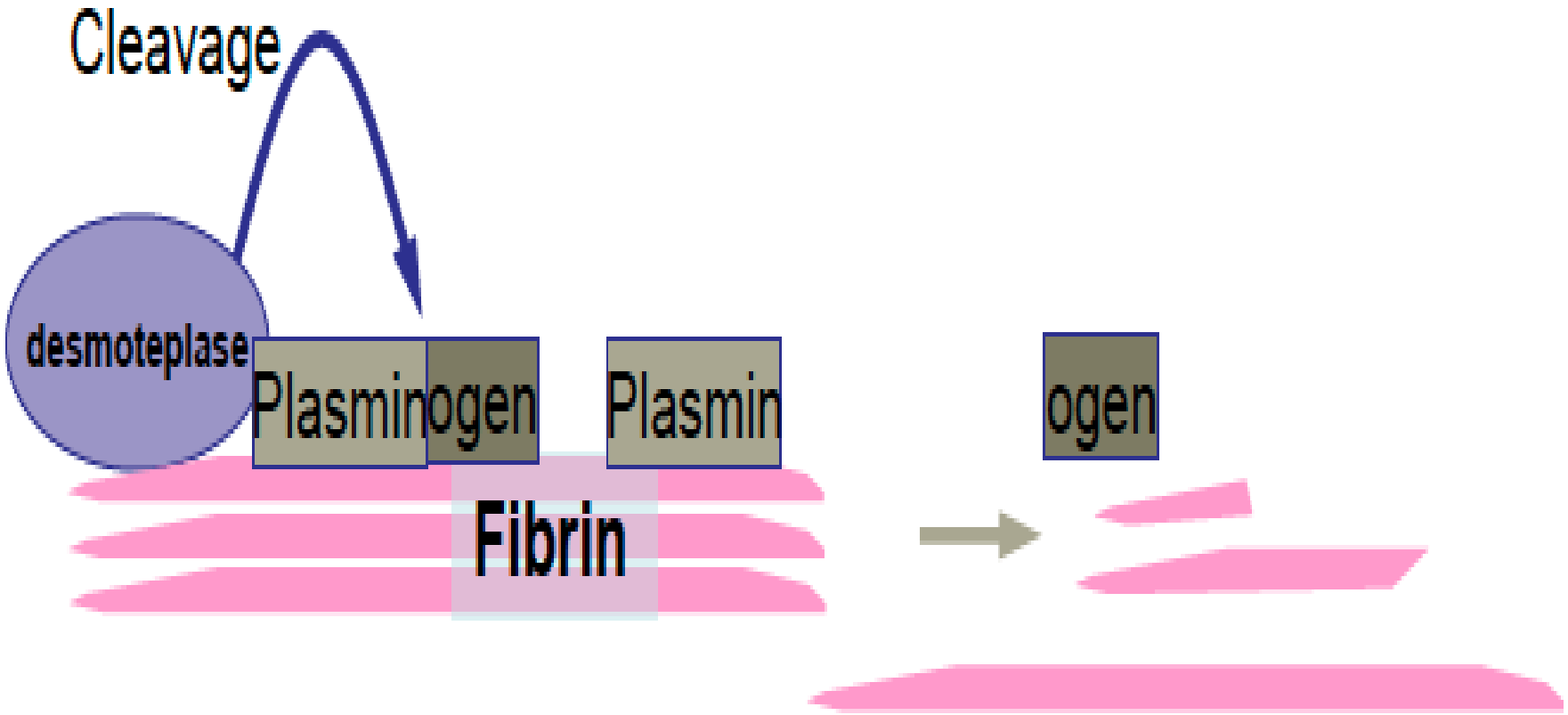
Agent	Half-life (min	Fibrin selectivity	PAI-1 inhibition
Urokinase	15	-	+++
Alteplase	4-8	++	+++
Staphylokinase	6	---	-
Monteplase	23	+/-	+++
Pamiteplase	30-47	++	+++
Lanoteplase	23-37	+	-
Reteplase	14-18	+	++
Tenecteplase	11-20	+++	-
Desmoteplase	138	+++++	?

Coagulopatia da tPA

- Dovuta alla non alta selettività del tPA per la fibrina del trombo, con conseguente degradazione del fibrinogeno in circolo e secondaria ipofibrinogenemia



Desmoteplase



Desmoteplase

Potential Advantages

	Alteplase	Desmoteplase	Desmoteplase advantages
Administration time after stroke onset	0-3h	3-9h	Broader time-window larger patient potential
Neurotoxicity	Yes	No	Survival of brain tissue
Fibrin selectivity **Fibrin specificity** **BBB damage**	72x over Fibrinogen 550x over absence Yes	12,900x over Fibrinogen 105,000x over absence No	Lower bleeding risk
Activation by ß-Amyloid	Yes	No	Lower bleeding risk in the elderly
Administration	i.v. infusion	Single bolus, i.v.	Ease of administration
Half life	3-5 min	About 4.5h	Positive impact on re-occlusion rate and formation of micro-emboli

DIAS-3 (DIAS-4, DIAS-J)

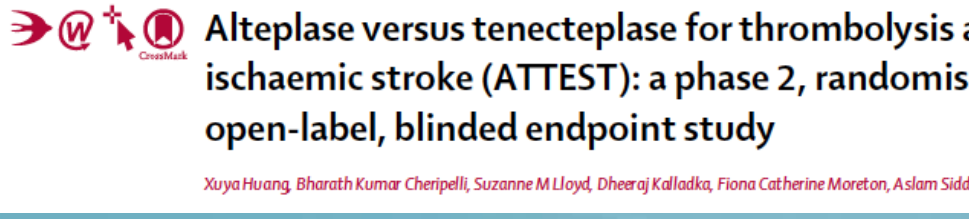
Safety and efficacy of desmoteplase given 3–9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (DIAS-3): a double-blind, randomised, placebo-controlled phase 3 trial

Gregory W Albers*, Rüdiger von Kummer*, Thomas Truelsen, Jens-Kristian S Jensen, Gabriela M Rava, Bjørn A Grønning, Hugues Chabriat, Ku-Chou Chang, Antonio E Davalos, Gary A Ford, James Grotta, Markku Kaste, Lee H Schwamm, Ashfaq Shuaib, for the DIAS-3 Investigators†

Albers G. et al. Lancet Neurol 2015

Tenecteplase

- TNK-S2B (USA, TNK vs rtPA, stopped)
- ATTEST (UK, TNK vs rtPA, <4.5h)
- NOR-TEST (Norvegia, BMC 2014, TNK vs rtPA)
- TEMPO-1, TEMPO-2 (Calgary, NIHSS<6, CTA/CTP occlusion, <12h)
- Parsons et al. NEJM 2015: Australia, fase2b (TNK vs rtPA, <6h)


Alteplase versus tenecteplase for thrombolysis a
ischaemic stroke (ATTEST): a phase 2, randomis
open-label, blinded endpoint study

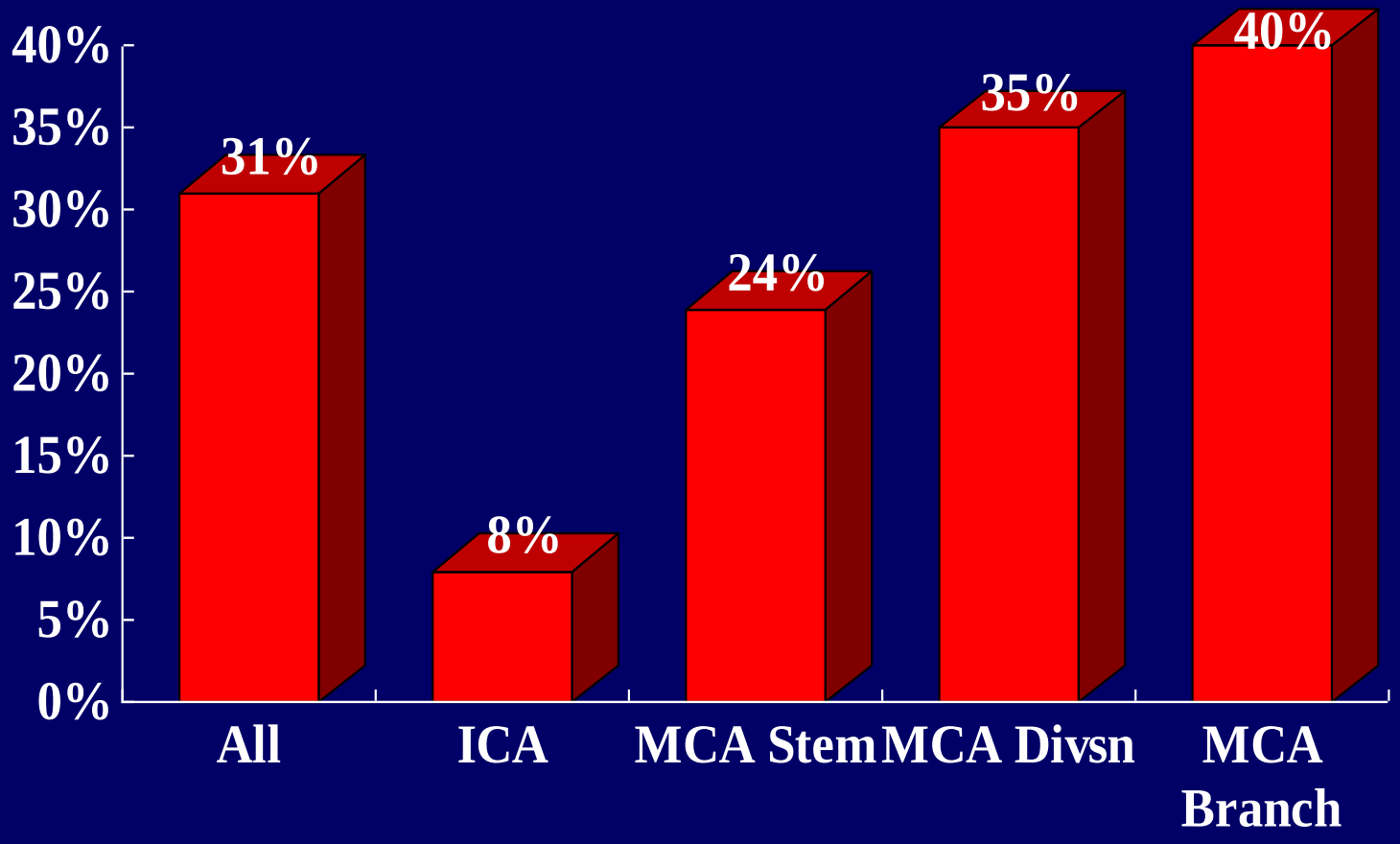
Xuya Huang, Bharath Kumar Cheripelli, Suzanne M Lloyd, Dheeraj Kalladka, Fiona Catherine Moreton, Aslam Sidd


A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke

Mark Parsons, M.D., Neil Spratt, M.D., Andrew Bivard, B.Sc., Bruce Campbell, M.D., Kong Chung, M.D., Ferdinand Miteff, M.D., Bill O'Brien, M.D., Christopher Bladin, M.D., Patrick McElduff, Ph.D., Chris Allen, M.D., Grant Bateman, M.D., Geoffrey Donnan, M.D., Stephen Davis, M.D., and Christopher Levi, M.D.

EFFICACIA

i.v t-PA recanalization at one hour (angiographic data)



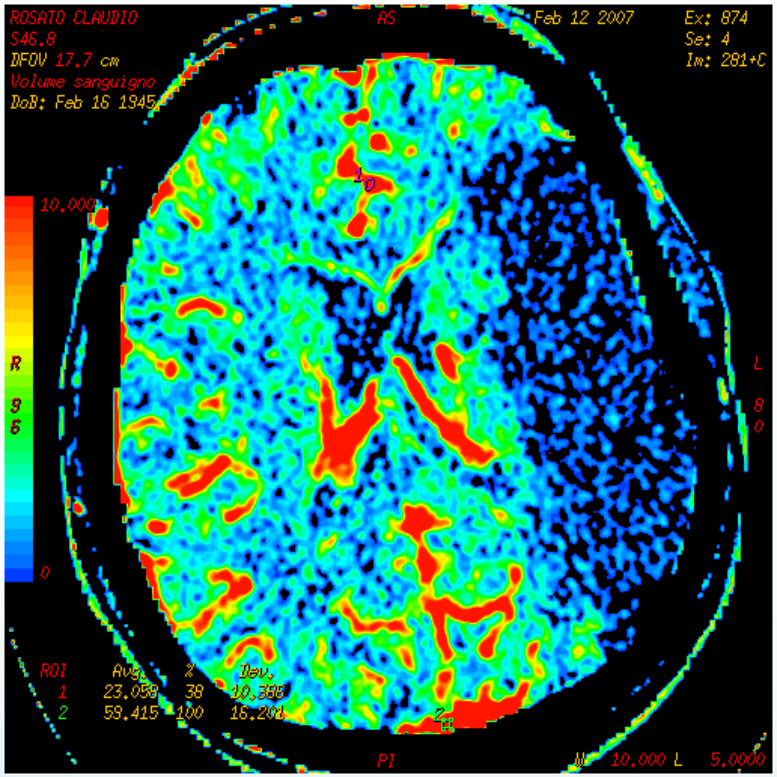
Del Zoppo et al., Ann Neurol 1993

RICANALIZZAZIONE

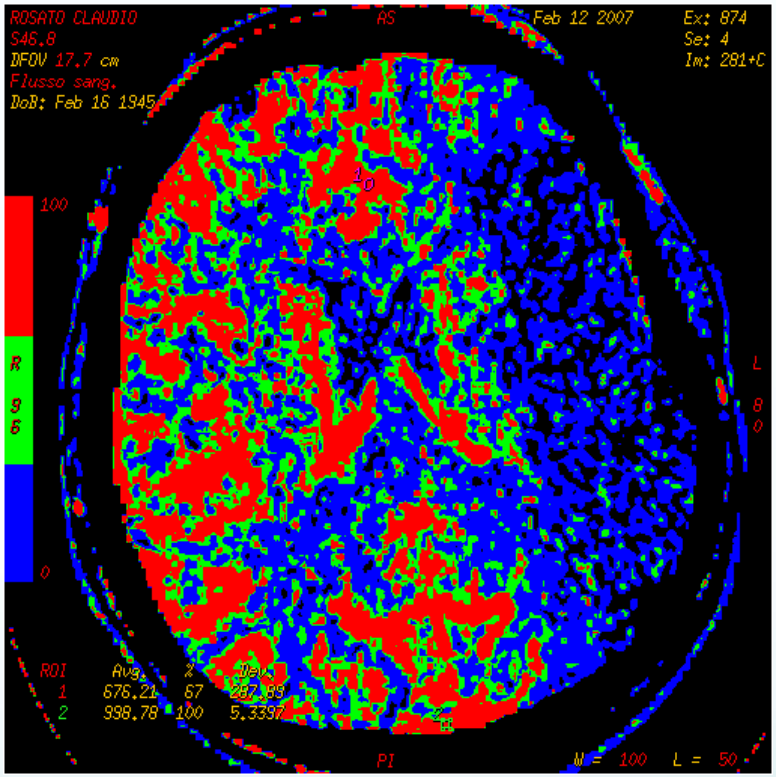
≠

RIPERFUSIONE

Caso

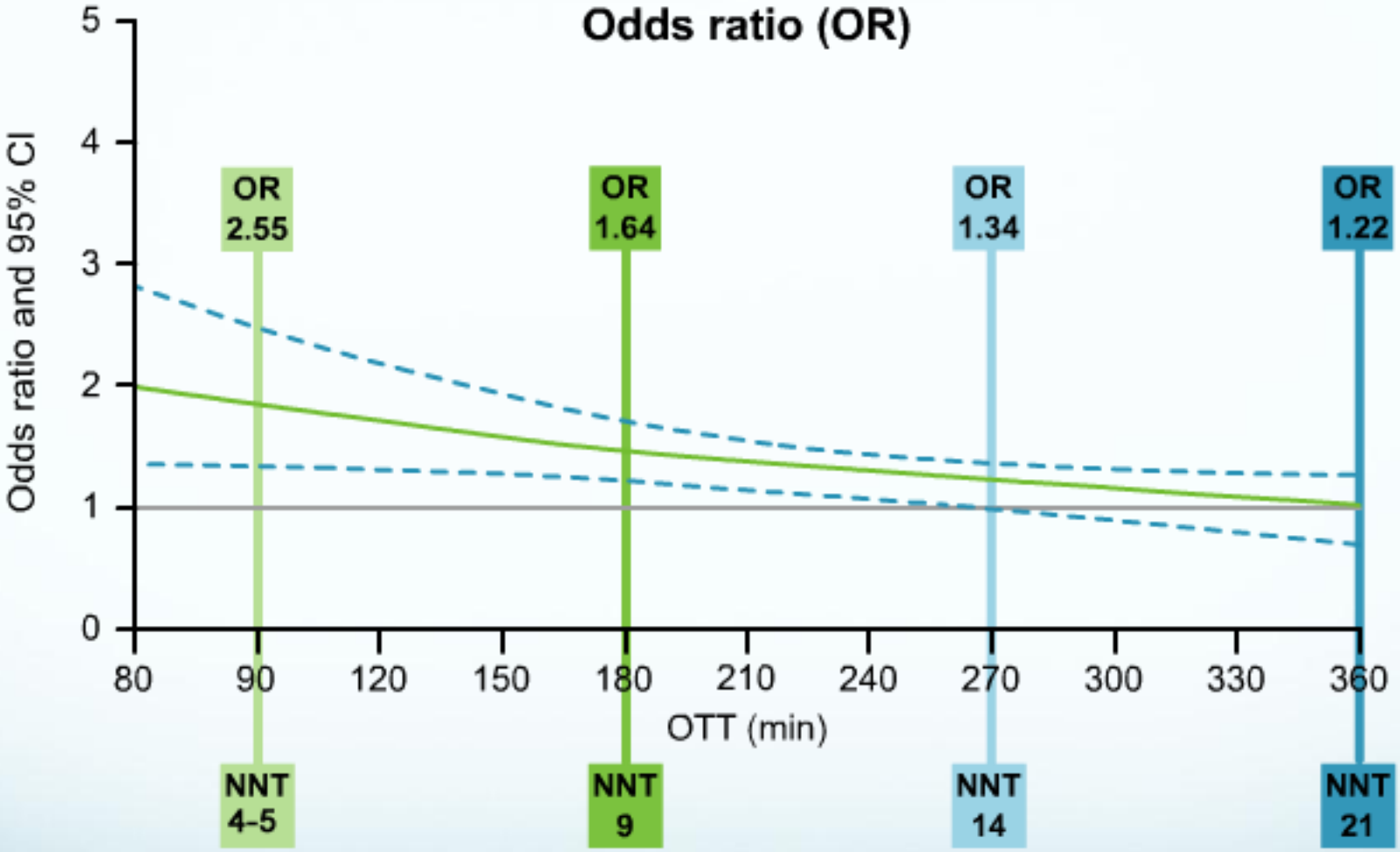


CBV



CBF

2h 30’



NNT, Number needed to treat
OTT, onset to treatment time
mRS, modified Rankin Score

TRIALS REGISTRATIVI

NINDS study

The New England
Journal of Medicine

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Volume 333 DECEMBER 14, 1995 Number 24

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

- 1991-1994
- <3h
- O,9 mg/Kg, 10% bolo, infusione in 60’

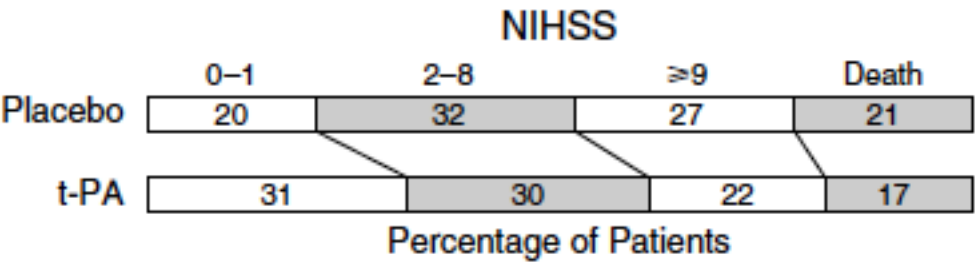
NINDS rtPA Stroke Study Group NEJM 1995

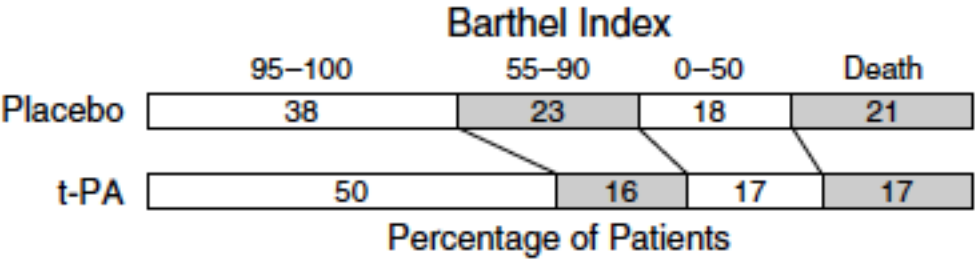
NINDS study

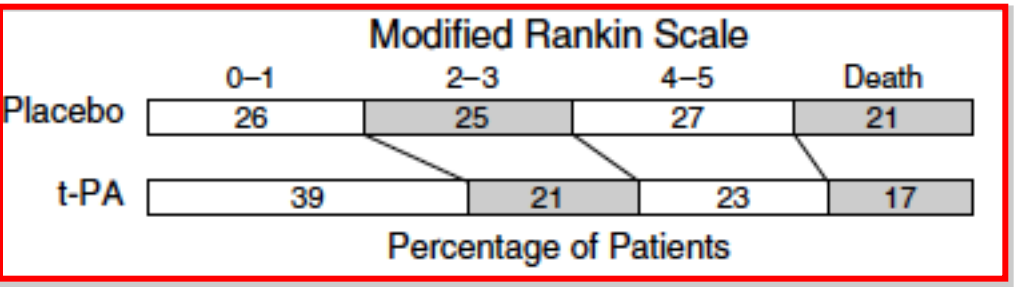
Table 2. Base-Line Characteristics of the Patients in the Two Parts of the Study, According to Treatment Group.*

Characteristic	Part 1		Part 2	
	t-PA (N = 144)	Placebo (N = 147)	t-PA (N = 168)	Placebo (N = 165)
Age (yr)	67±10	66±11	69±12	66±13
Race or ethnic group (%)				
White, non-Hispanic	62	61	69	66
Black	29	31	23	26
Hispanic	8	5	5	7
Asian	1	0	3	1
Other	0	3	1	1
Female sex (%)	42	40	43	42
Weight (kg)	76±15	80±18	76±16	80±21
NIHSS score				
Median	14	14	14	15
Minimum	1	1	2	2
Maximum	37	32	37	33
Stroke subtype (%)				
Small-vessel occlusive	19	11	14	9
Cardioembolic	42	44	45	44
Large-vessel occlusive	35	42	39	45
Other	3	3	2	3
Blood pressure (mm Hg)				
Systolic	155±22	153±20	153±22	152±21
Diastolic	85±12	85±13	85±14	86±15
Fibrinogen (mg/dl)	332±94	349±106	311±102	316±86
Glucose (mg/dl)†	149±76	152±78	149±66	149±78
CT findings (%)				
Edema	5	3	4	6
Mass effect	3	2	3	4

NINDS rtPA Stroke Study Group NEJM 1995







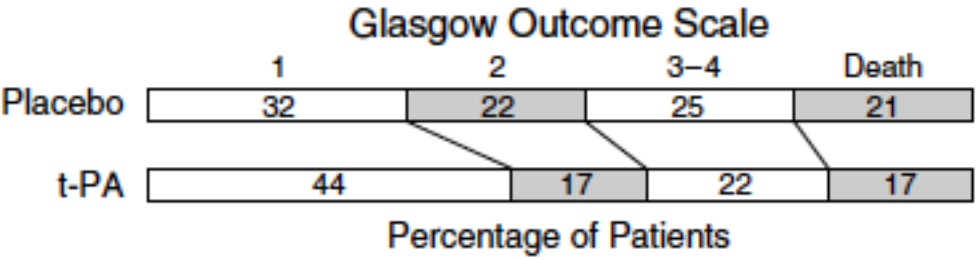


Figure 2. Outcome at Three Months in Part 2 of the Study, According to Treatment.

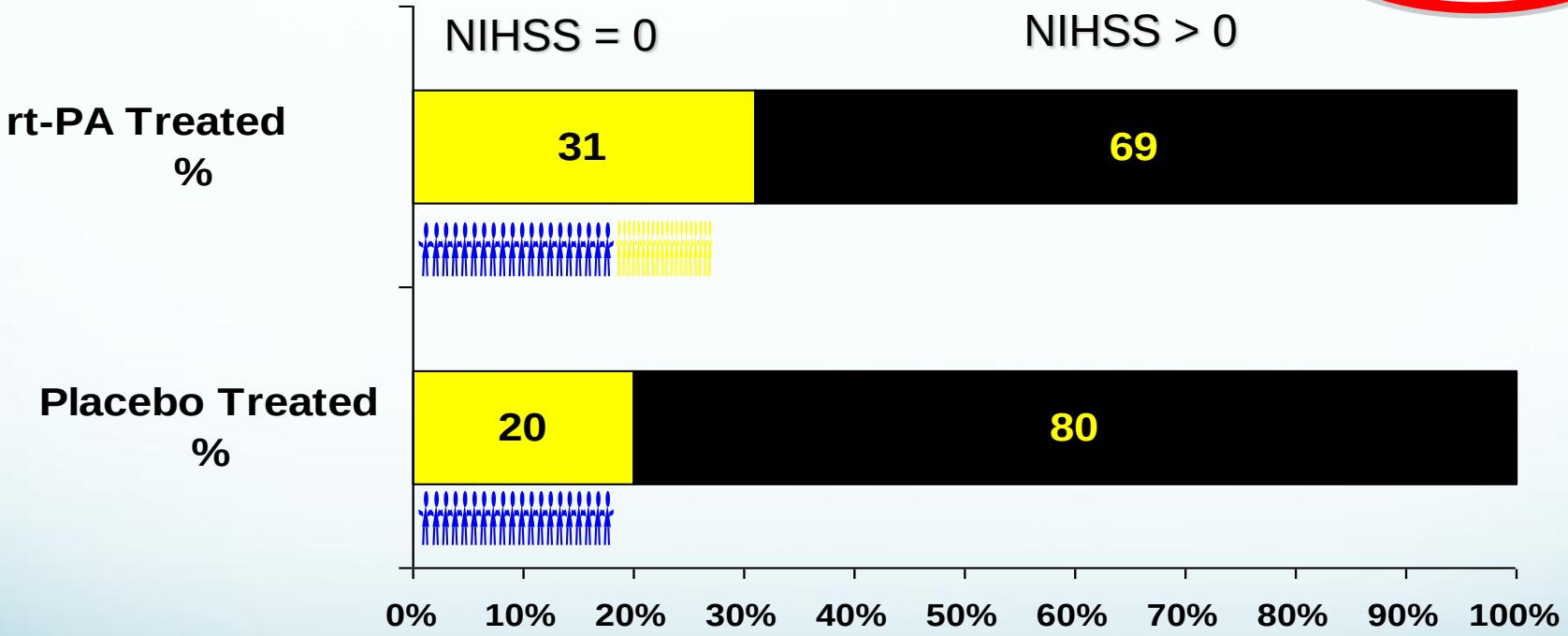
Table 6. Incidence of Intracranial Hemorrhage within 36 Hours of Treatment for Stroke.

Type of Intracranial Hemorrhage	t-PA	Placebo
	no. (%)	
Part 1	144	147
Symptomatic	8 (6)	0
Fatal*	4	0
Nonfatal	4	0
Asymptomatic	5 (3)	3 (2)
Part 2	168	165
Symptomatic	12 (7)	2 (1)
Fatal*	5	1
Nonfatal	7	1
Asymptomatic	9 (5)	6 (4)

*Values include all deaths attributed to hemorrhage.

TROMBOLISI EV
studio NINDS

NINDS Investigators NEJM, 1995

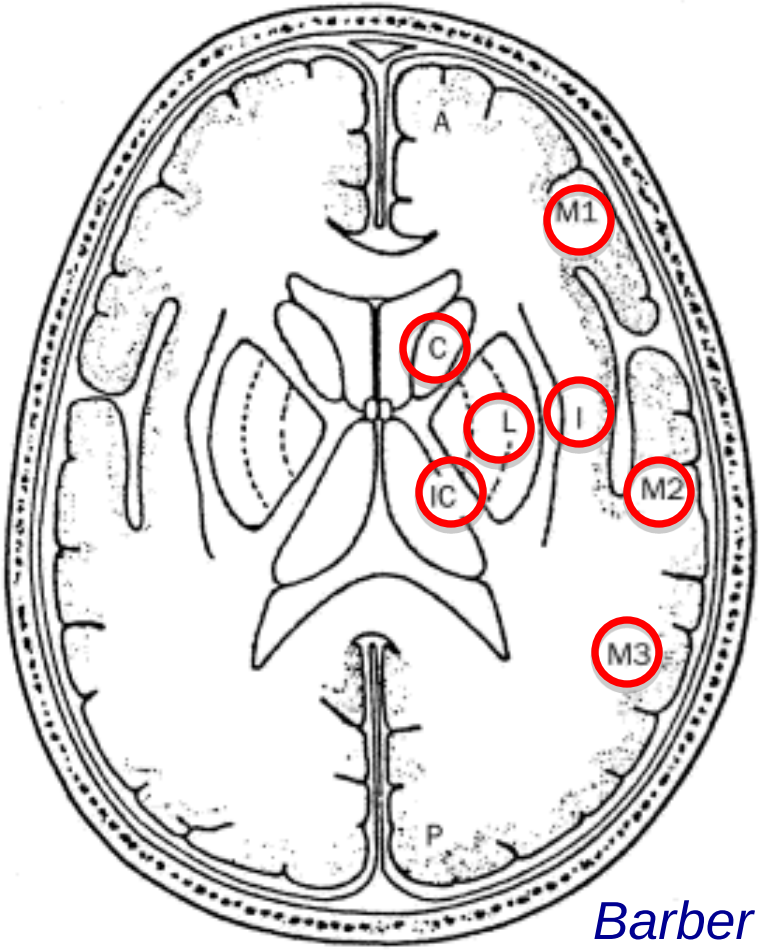


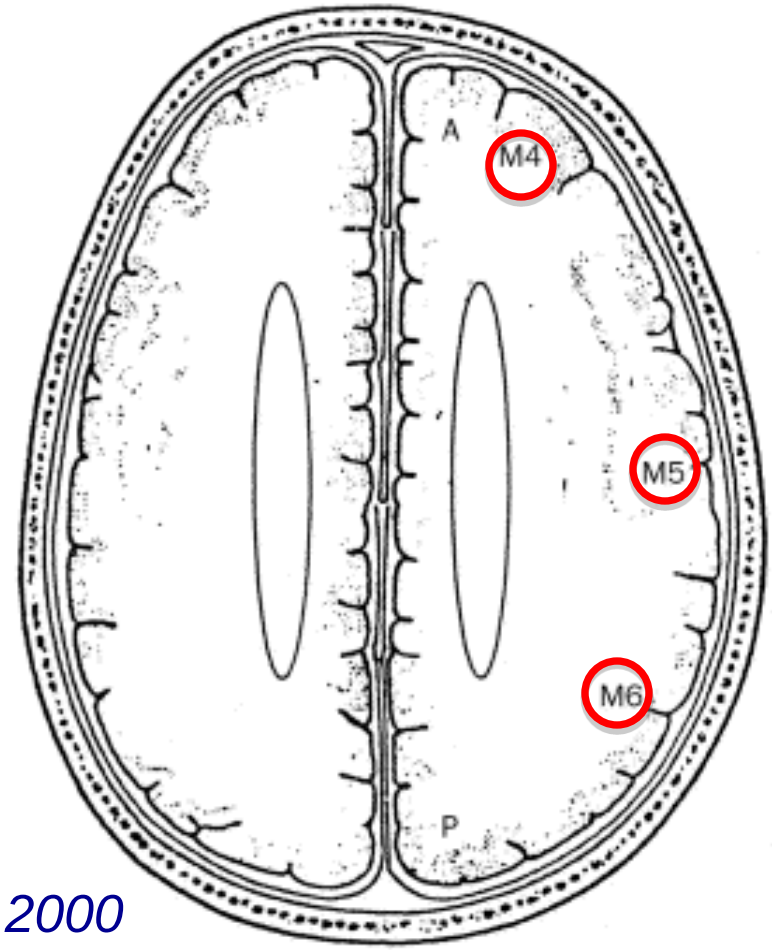
NIHSS at 90 Days: complete recovery

Criteri TC encefalo

ASPECTS score

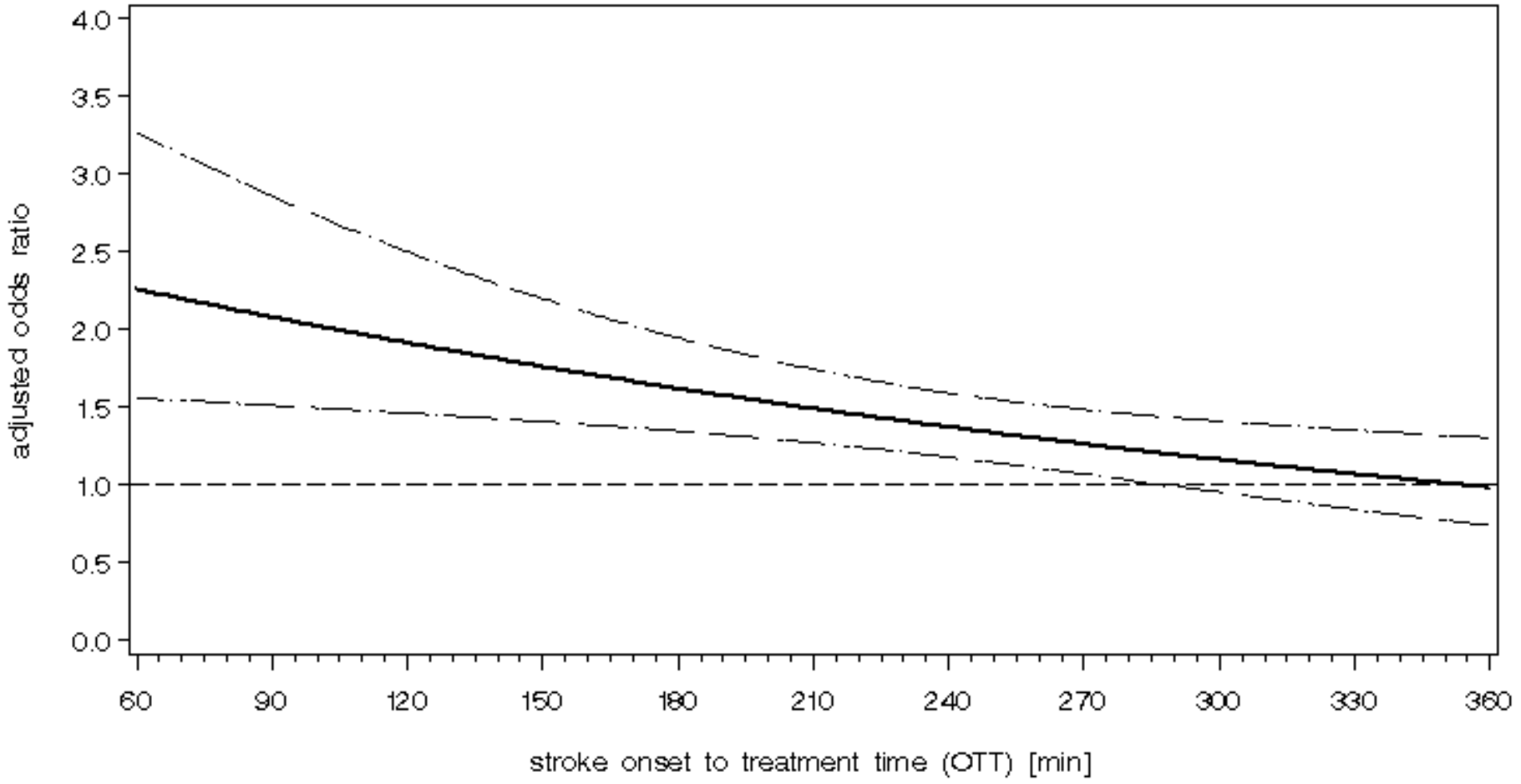
Alberta Stroke Programme Early CT Score





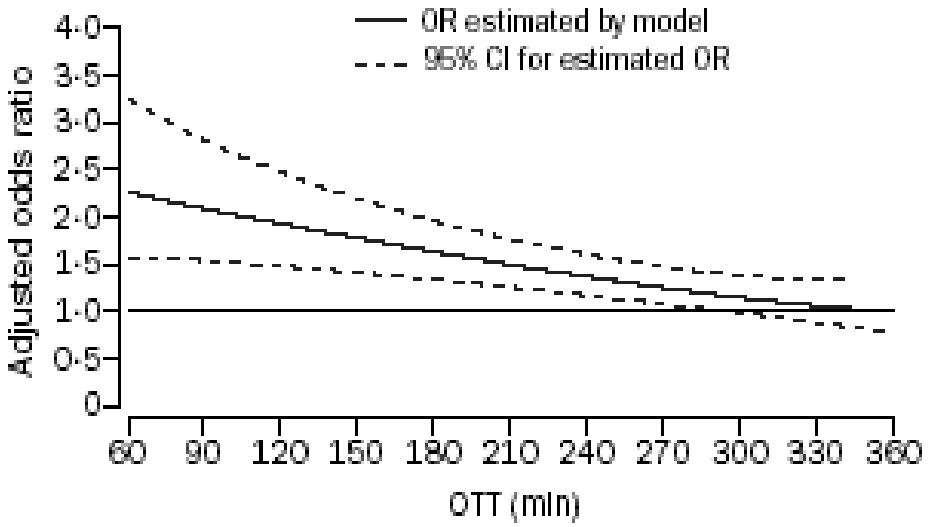
Barber PA, Lancet 2000

Trombolisi con r-tPA nell'ictus ischemico acuto



Randomized placebo-controlled alteplase trial

Trial	Numero pazienti	"Time window"
NINDS parte 1	291	0-90
NINDS parte 2	333	91-180
ECASS I	620	0-360
ECASS II	800	0-360
ATLANTIS A	142	0-360
ATLANTIS B	613	180-300
Totale pz	2775	



Il trattamento precoce con t-PA entro 3 ore è associato a un buon outcome a 3 mesi. Esiste però anche un potenziale beneficio dopo le 3 ore

The ATLANTIS, ECASS and NINDS rt-PA Study Group, Lancet 2004

Approvazione rtPA

- USA (FDA) nel 1996
- CANADA nel 1999
- Europa nel….

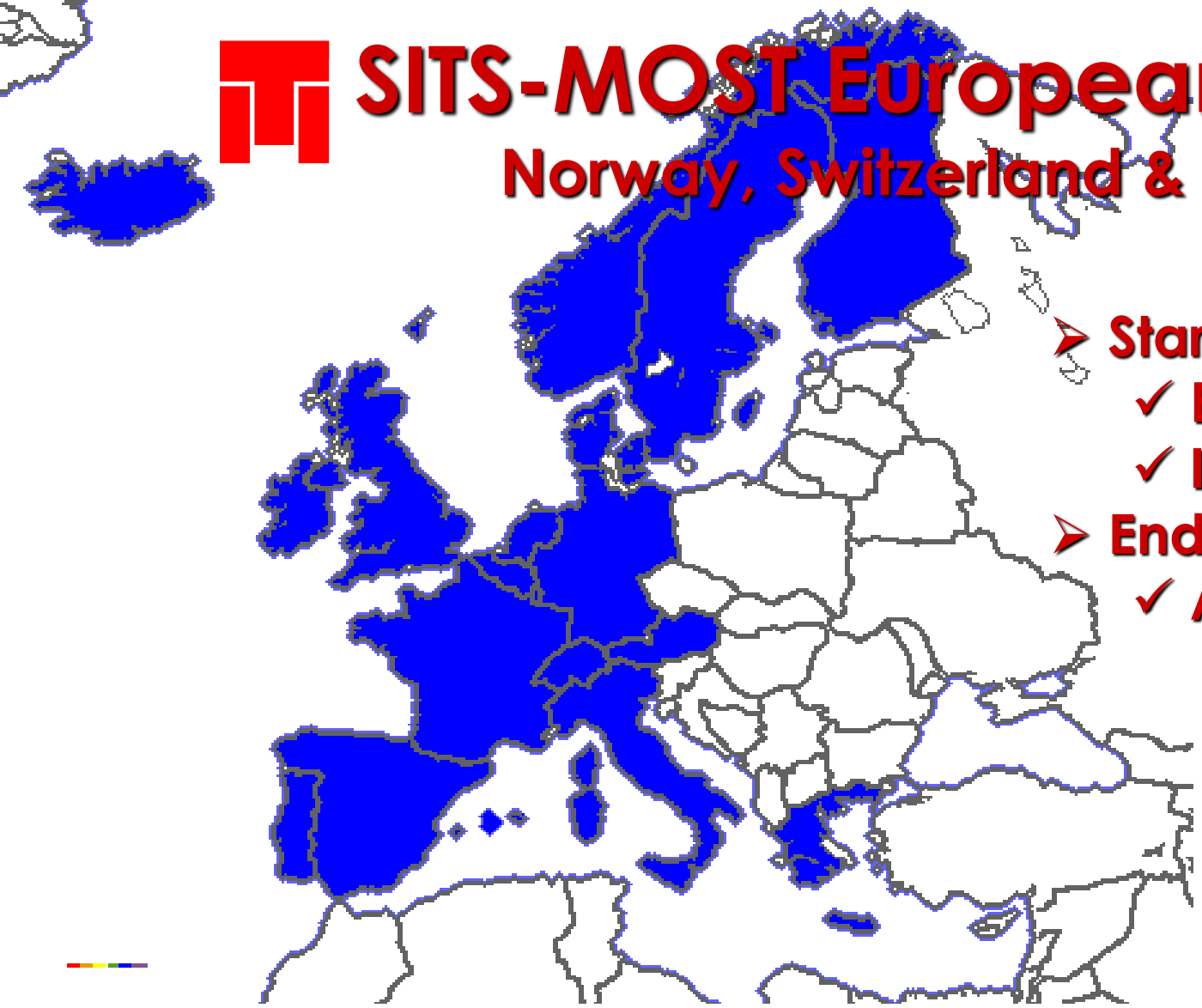
Fasi dell'approvazione del t-PA in Europa Decisione dell'EMEA (Settembre 2002)

- Autorizzazione all'immissione in commercio di Alteplase per il trattamento trombolitico dell'ictus ischemico entro 3 ore dall'esordio dei sintomi purché vengano effettuati (a cura della B.I.):
  - ✓ studio di monitoraggio post-marketing: SITS-MOST
  - ✓ studio randomizzato/controllato nella finestra 3-4 ore: ECASS III

AIC in Italia: D.M. 24 luglio 2003 G.U. N° 190 18 Agosto 2003

SITS-MOST European Union +

Norway, Switzerland & Iceland



- Start:
  - ✓ Europe: Jan 2003
  - ✓ Italy: Mar 2004
- End:
  - ✓ All: Apr 2006

N°	participant Countries	14
N°	active centres	287
N°	treated patients	6483

SITS-MOST: Study outline - 1

- Clinical phase: **IV**
- Inclusion/exclusion criteria: same as those of RCTs (reported in the SPC)
- Drug dose: 0.9 mg/kg bw, 10% bolus /1 min
- Data included at baseline
  - ✓ patient demographics
  - ✓ timing of procedures
  - ✓ neurological status by NIHSS
  - ✓ imaging results before treatment

Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study

Nils Wahlgren, Niaz Ahmed, Antoni Dávalos, Gary A Ford, Martin Grond, Werner Hacke, Michael G Hennerici, Markku Kaste, Sonja Kuelkens, Vincent Larrue, Kennedy R Lees, Risto O Roine, Lauri Soinne, Danilo Toni, Geert Vanhooren, for the SITS-MOST investigators

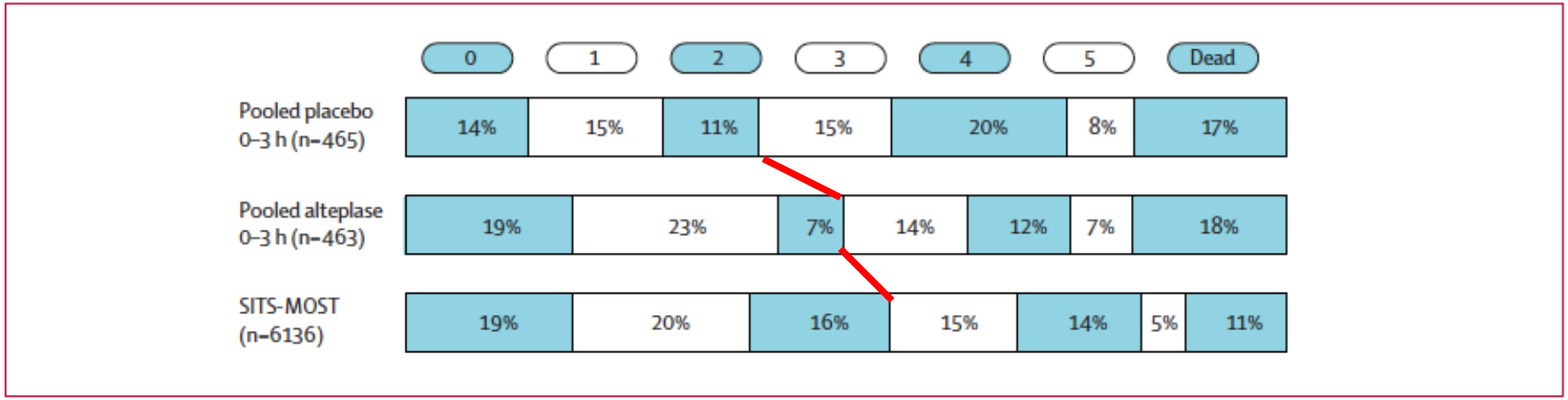


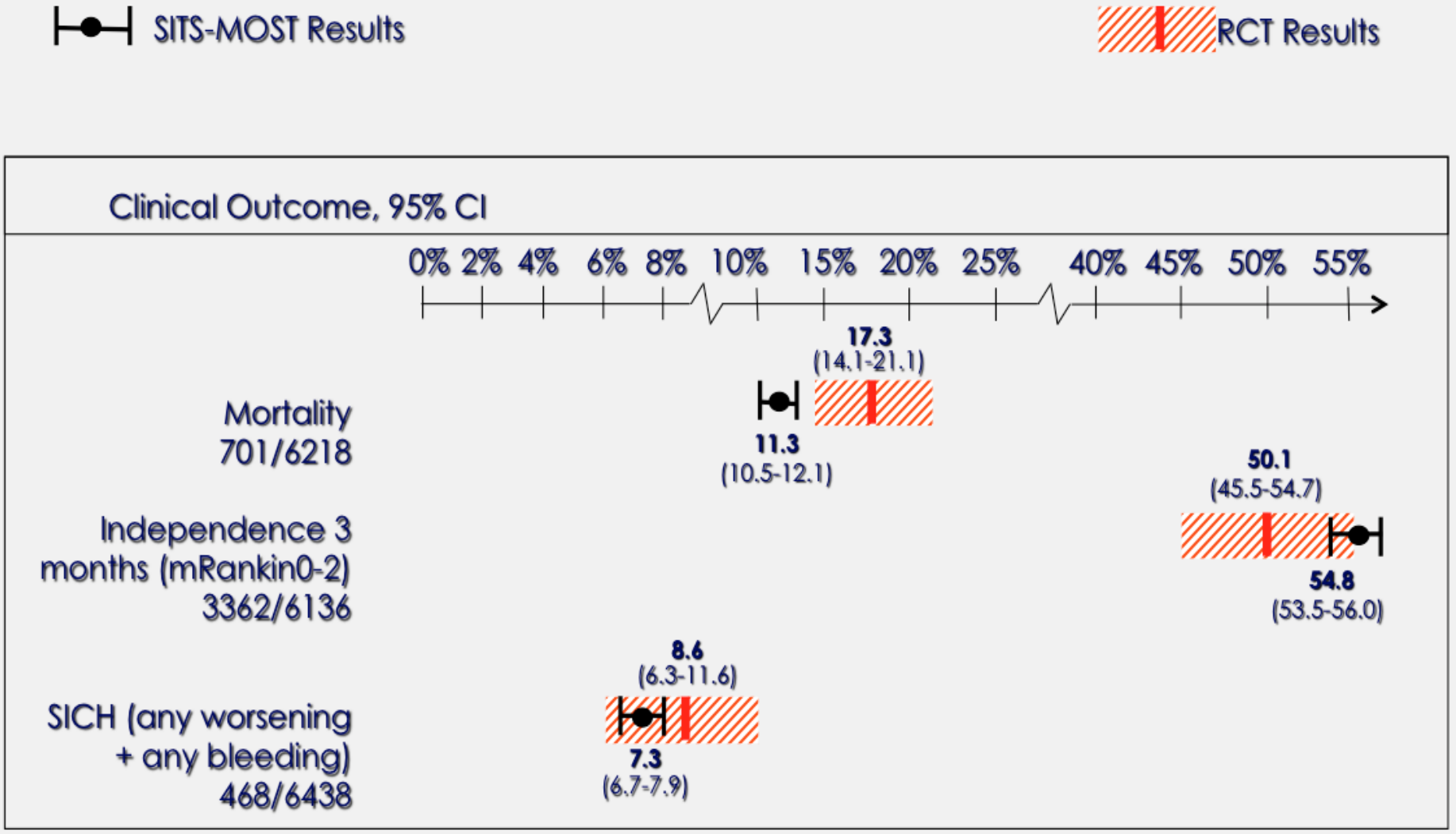
Figure 4: **Proportion of patients with modified Rankin score of 0–6 at 3 months in SITS-MOST and in pooled randomised controlled trials for both placebo and alteplase patients[2]**

Lancet 2007

Results: baseline

Variables	SITS-MOST N=6483	RCT Placebo N = 465	RCT t-PA N=464
Age, mean	68 (59-75)	67 (59-74)	69.6 (61-75)
% females	39.8	40.2	40.1
NIHSS, mean	12 (8-17)	14 (9-19)	13 (8-18)
Hypertension	58.7	60.7	59.7
Diabetes	16.0	18.9	21.1
AF	23.9	20.0	20.7
CHF	7.5	15.3	13.2
Previous stroke	10.1	12.7	13.8
Aspirin	29.8	28.8	36.4
Blood glucose, mg/dl	116 (102-140)	124 (106-151)	119 (104-158)
SBP, mmHg	150 (137-166)	152 (140-170)	156 (140-170)
DBP, mmHg	81 (74-90)	86 (77-95.5)	84 (78-92)

SITS-MOST: main outcomes compared with active arms of RCTs (proportions and 95% C.I.)



AGENZIA ITALIANA DEL FARMACO
DETERMINAZIONE 16 Novembre 2007
(Determinazione n. 1/AE) (*GU n. 278 del 29-11-2007*)

- Conferma:
  - ✓ necessità di proseguire registrazione pazienti nel SITS-ISTR
  - ✓ processo di accreditamento con le modalità seguite per SITS-MOST
  - ✓ utilizzo di actilyse
    - secondo informazioni in scheda tecnica
    - solo in stroke units, come definite da decreto A.I.C. 24 luglio 2003
  - ✓ Identificazione/implementazione dei centri da parte di Regioni e Province Autonome
  - ✓ richiesta di partecipazione al registro SITS-ISTR da fare al sito www.acutestroke.org
  - ✓ indicazione a registrare tutti i trattamenti
  - ✓ Coordinatore nazionale

- Precisa:
  - ✓ possibilità di accedere a consulenza neurochirurgica anche per via telematica
  - ✓ introduzione di Coordinatori regionali

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*

- 2003-2007
- 821 pts (19 paesi, 130 centri)

NEJM 2008

ECASS 3

Table 1. Major Inclusion and Exclusion Criteria.

Main inclusion criteria
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
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

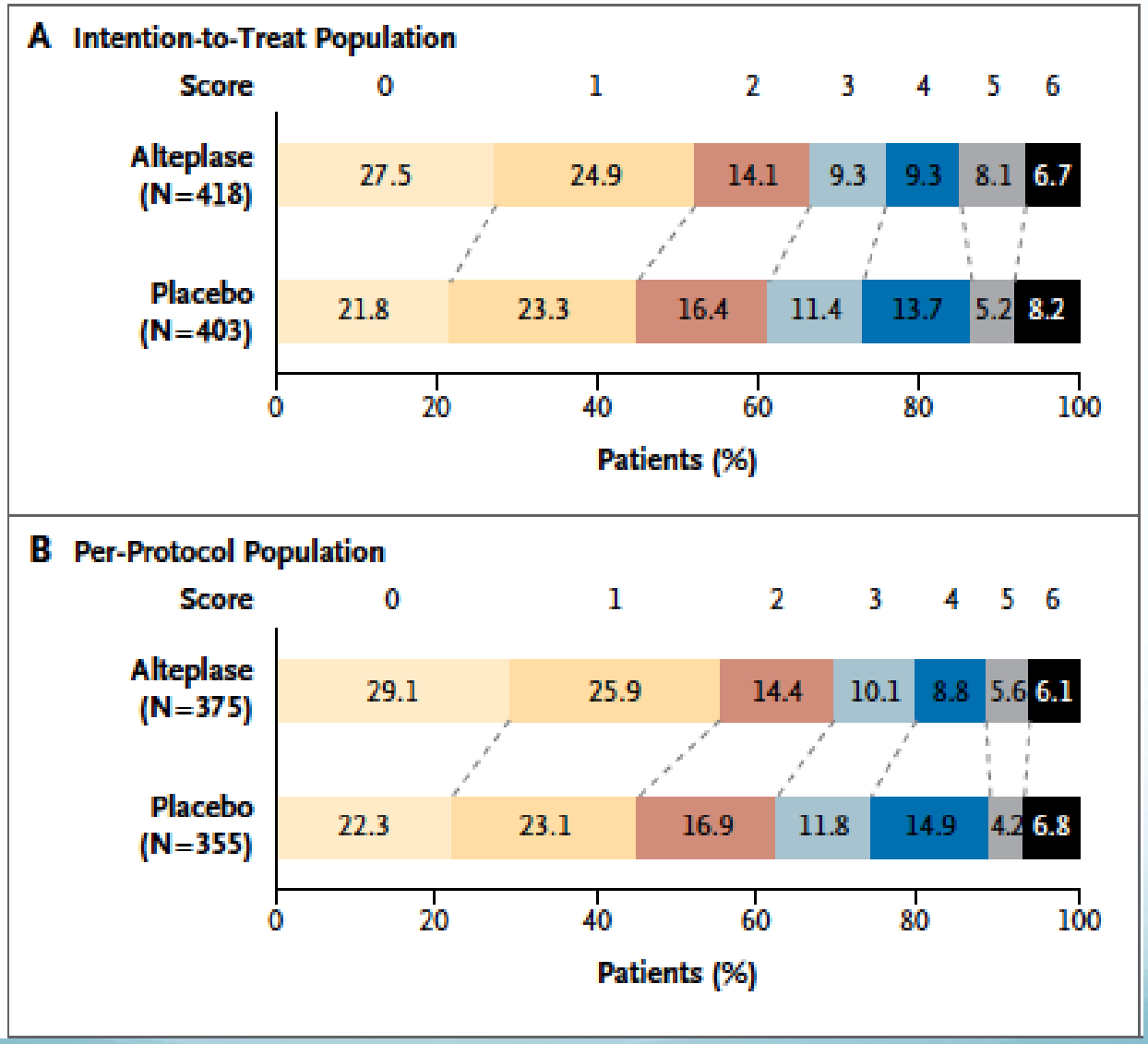
NEJM 2008

ECASS 3

	Day 90			
	Intention-to-Treat Population		Per-Protocol Population	
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*
mRS score of 0 or 1†	1.34 (1.02–1.76)	0.04	1.47 (1.10–1.97)	0.001
mRS score of 0–2	1.30 (0.95–1.78)	0.11	1.41 (1.01–1.96)	0.04
Barthel Index score ≥95‡	1.23 (0.93–1.62)	0.15	1.33 (0.99–1.80)	0.06
NIHSS score of 0 or 1, or >8-point improvement from baseline§	—		—	
[illegible]				
mRS score of 0 or 1	219 (52.4)	182 (45.2)	1.34 (1.02–1.76)	0.04†
Barthel Index score ≥95**	265 (63.4)	236 (58.6)	1.23 (0.93–1.62)	0.16†
NIHSS score of 0 or 1††	210 (50.2)	174 (43.2)	1.33 (1.01–1.75)	0.04†
GOS score of 1‡‡	213 (51.0)	183 (45.4)	1.25 (0.95–1.64)	0.11†

NEJM 2008

ECASS 3



NEJM 2008

Implementation and outcome of thrombolysis with alteplase 3–4·5 h after an acute stroke: an updated analysis from SITS-ISTR

*Niaz Ahmed, Nils Wahlgren, Martin Grond, Michael Hennerici, Kennedy R Lees, Robert Mikulik, Mark Parsons, Risto O Roine, Danilo Toni, Peter Ringleb, for the SITS investigators**

Methods We compared 664 patients presenting with ischaemic stroke and given intravenous altepase (0·9 mg/kg total dose) between 3 h and 4·5 h with 11 865 patients treated within 3 h. All patients were otherwise compliant with European summary of product characteristics criteria and had been documented in the international stroke treatment registry between Dec 25, 2002, and Nov 15, 2007. Outcome measures were symptomatic intracerebral haemorrhage within 24 h (haemorrhage type 2 associated with National Institutes of Health Stroke Scale [NIHSS] ≥4 points deterioration), and mortality and independence (modified Rankin scale of 0–2) at 3 months.

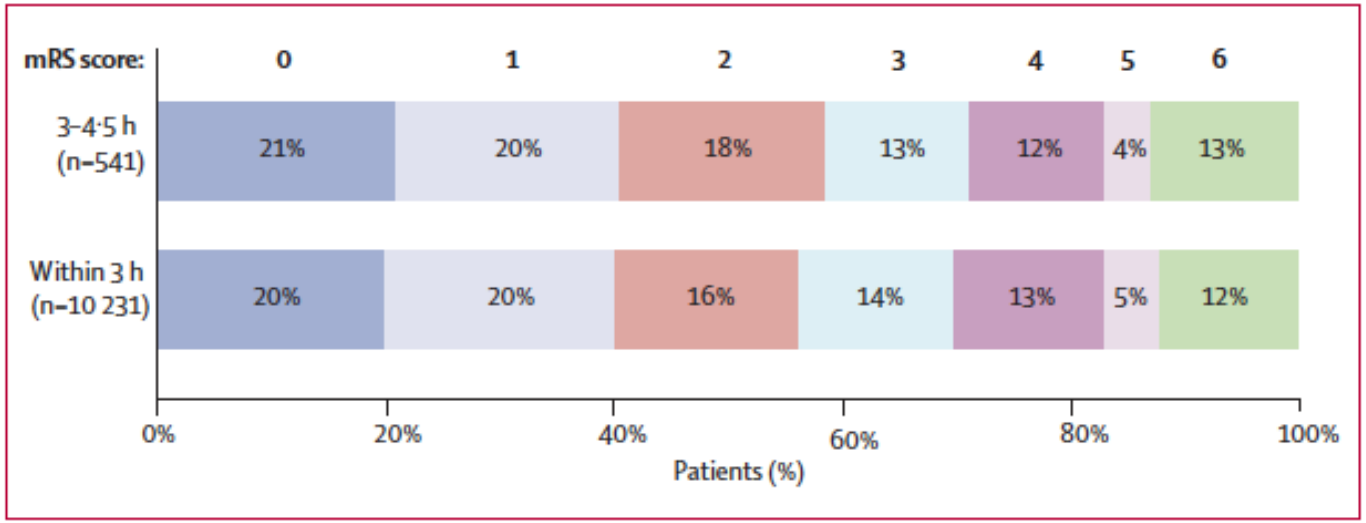
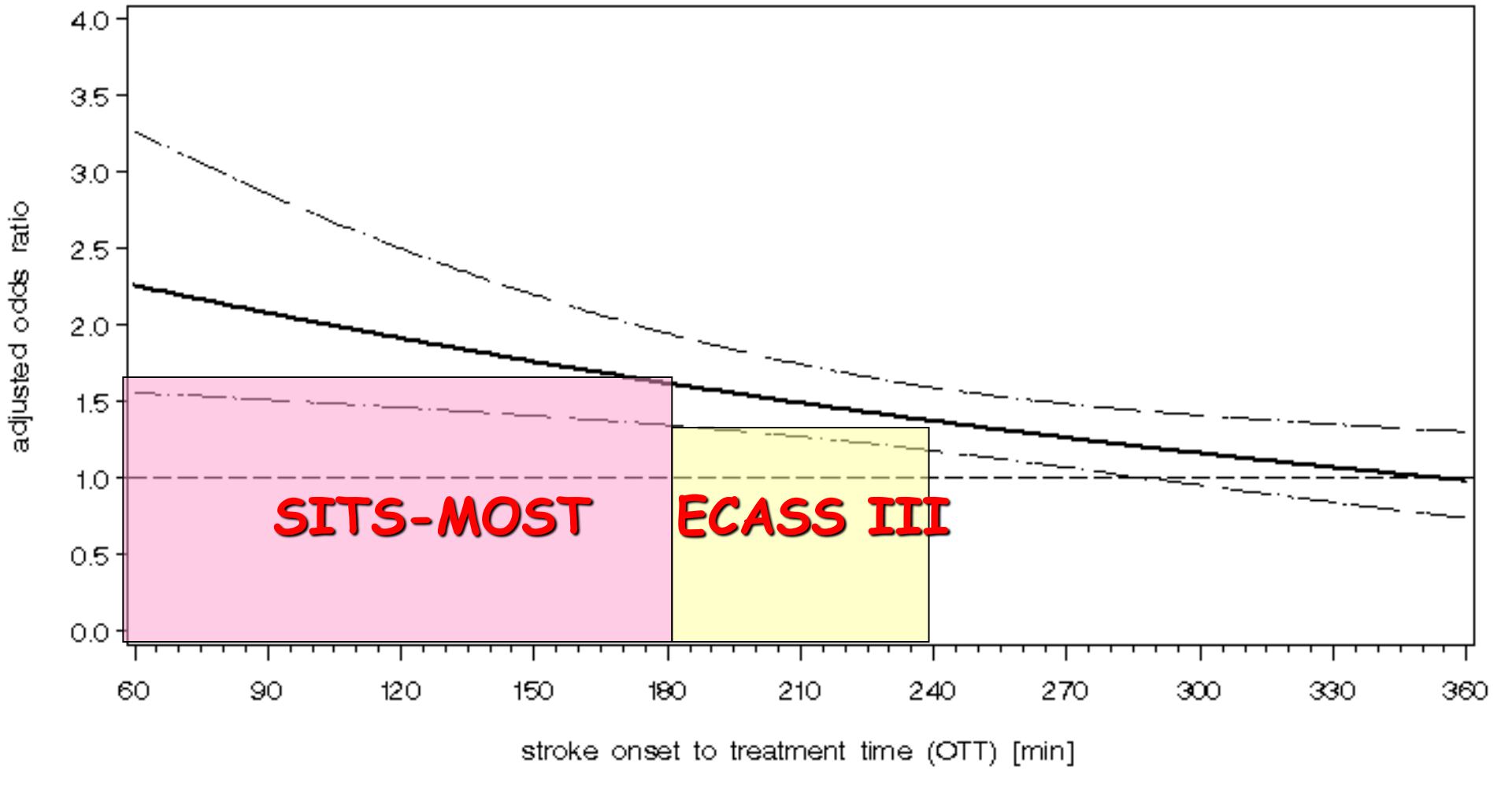


Figure 2: **Proportion of patients in the 3–4·5 h and within 3 h cohorts according to the modified Rankin scale (mRS) score at 3 months**

Lancet Neurol 2010

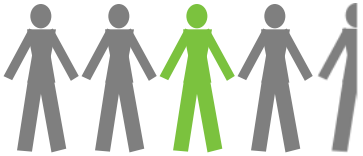
mRS 0-1 at Day 90

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



Thrombolysis: Number of Patients Needed to Treat (NNT) to Achieve Excellent Recovery (mRS 0-1)

≤ 90 mins

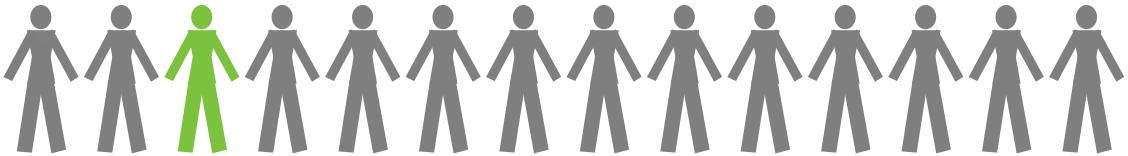


NNT=4 to 5

90 min - 3 h

NNT=9

3 - 4.5 h



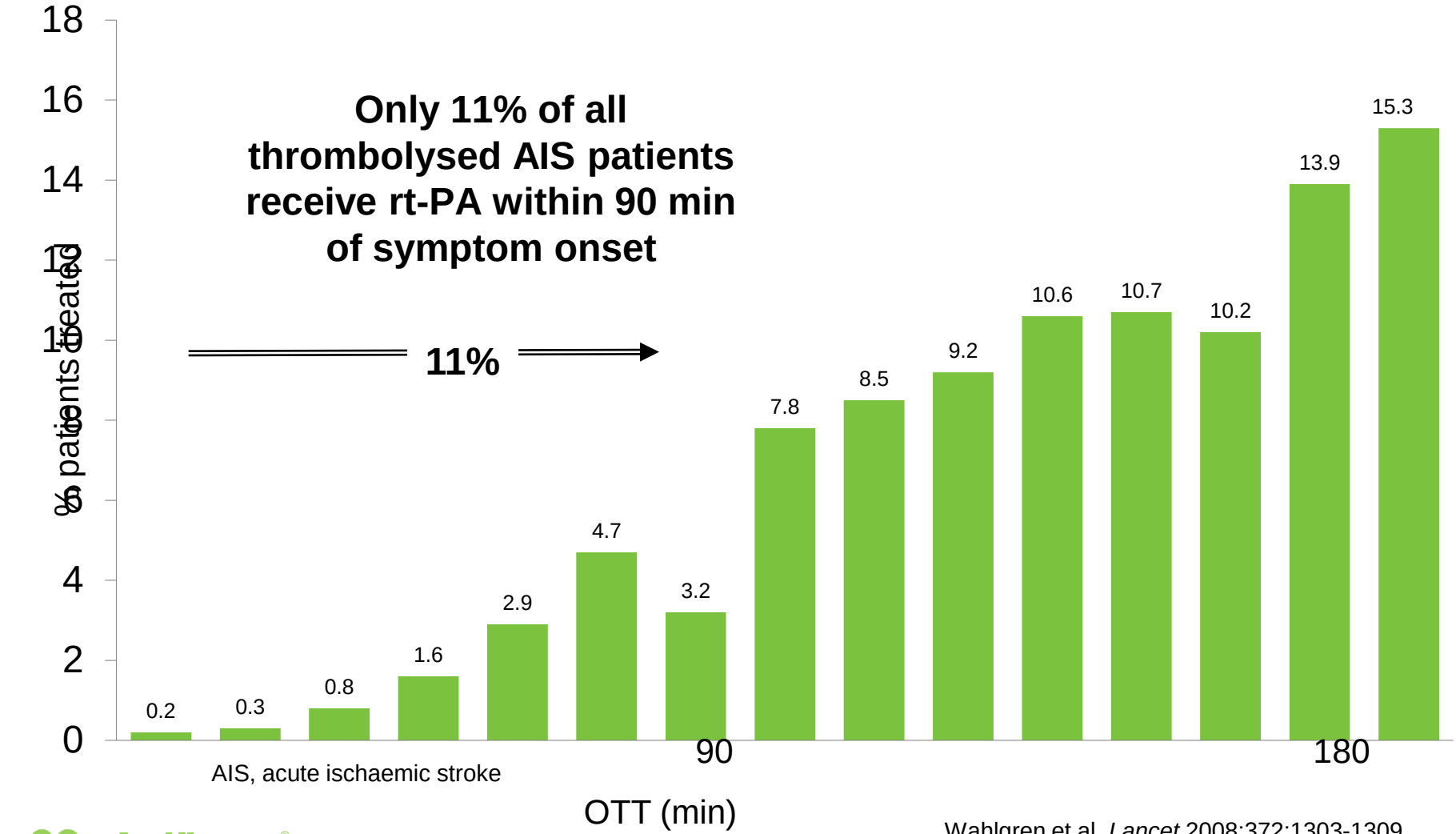
NNT=14

mRS, modified Rankin Scale

Actilyse® alteplase
Act FAST

Lees et al. *Lancet* 2010;375:1695-1703.

rt-PA Effects are Time Dependent



Wahlgren et al. *Lancet* 2008;372:1303-1309.
Lees et al. *Lancet* 2010;375:1695-1703.

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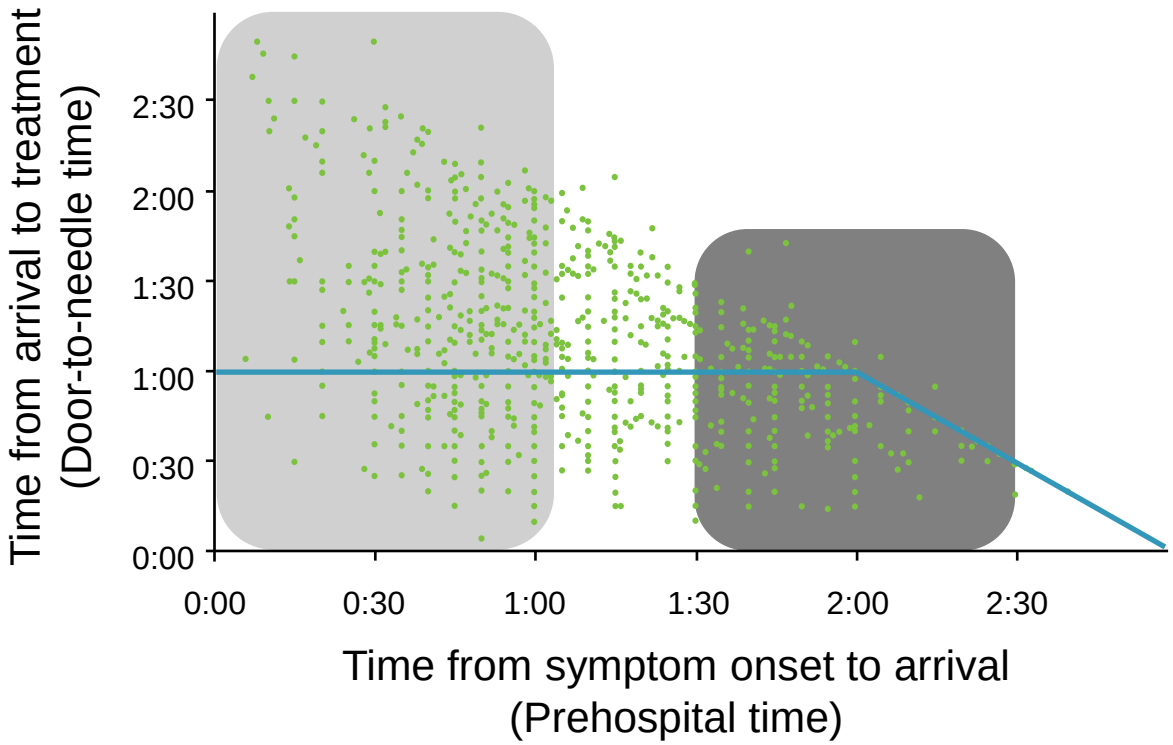
SITS: Door-to-Needle vs Time Window

Doctors who have more time, take more time, but the sooner thrombolysis is initiated, the greater the benefit



SITS-Database https://sitsinternational.org

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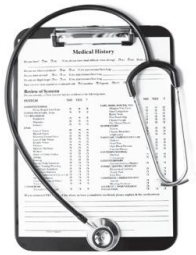
Raising Public Awareness

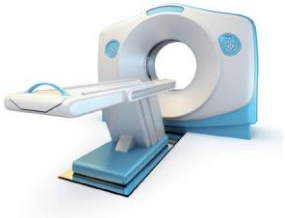
- Campaigns
  - Target the general public as stroke witnesses
  - Symptom awareness
  - Awareness to take action
- Keep the message easy
- The ultimate aim is to keep the time to treatment as short as possible
- Public awareness campaigns can increase ambulance dispatches for stroke

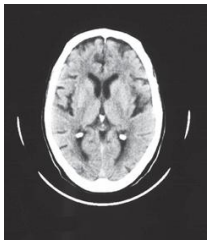
Example of a German stroke awareness campaign

NIH-recommended Emergency Department Response Times

DTN ≤60 min: the "golden hour" for evaluating and treating acute stroke







T=0
Suspected stroke patient arrives at stroke unit

≤10 min
Initial MD evaluation (including patient history, lab work initiation, & NIHSS)

IDEALLY performed prehospital

≤ 15 min
Stroke team notified (including neurologic expertise)

≤ 25 min
CT scan initiated

≤ 45 min
CT & labs interpreted

≤ 60 min
rt-PA given if patient is eligible

NINDS NIH website. Stroke proceedings. Latest update 2008.

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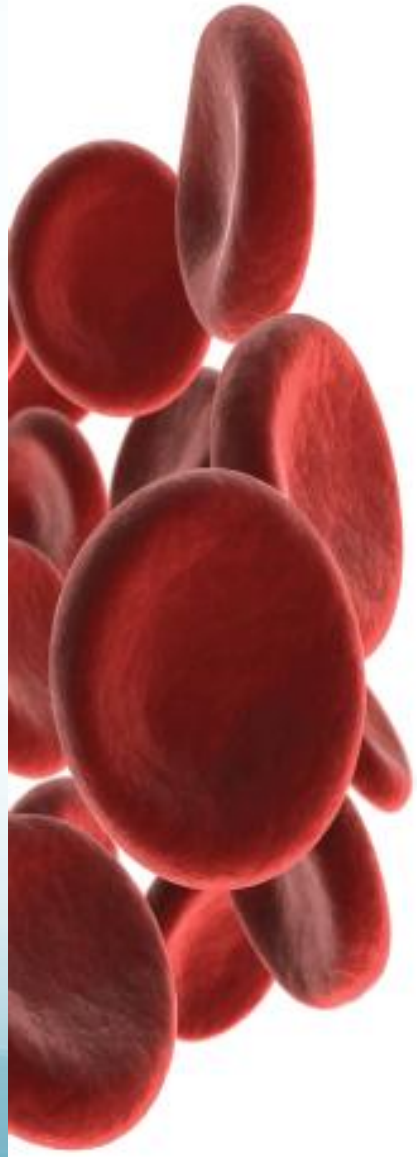
Door to Needle below 40 minutes



SITS WATCH - Project plan

Enhancing thrombolysis in acute stroke

Studio IST-3

Third International Stroke Trial

- studio indipendente, internazionale, multicentrico, randomizzato e controllato verso placebo finalizzato a rivalutare l'efficacia e la sicurezza dell'uso di rt-PA i.v. nei pazienti con ictus ischemico acuto entro 6 ore dall'esordio dei sintomi (3.100 pazienti, anni 2000-2011);
- i pazienti randomizzabili sono i seguenti:
  - Pazienti con età > 80 anni
  - Stroke lieve (NIHSS < 4) o con sintomi in rapido miglioramento

Authors' conclusions

Overall, thrombolytic therapy appears to result in a significant net reduction in the proportion of patients dead or dependent in activities of daily living. However, this appears to be net of an increase in deaths within the first seven to ten days, symptomatic intracranial haemorrhage, and deaths at follow-up at three to six months. The data from trials using intravenous recombinant tissue plasminogen activator, from which there are the most evidence on thrombolytic therapy so far, suggest that it may be associated with less hazard and more benefit. There was heterogeneity between the trials for some outcomes and the optimum criteria to identify the patients most likely to benefit and least likely to be harmed, the latest time window, the agent, dose, and route of administration, are not clear. The data are promising and may justify the use of thrombolytic therapy with intravenous recombinant tissue plasminogen activator in experienced centres in highly selected patients where a licence exists. However, the data do not support the widespread use of thrombolytic therapy in routine clinical practice at this time, but suggest that further trials are needed to identify which patients are most likely to benefit from treatment and the environment in which it may best be given. To avoid the problem of data missing from some trials for some key outcomes encountered in this review to date, and to assist future metaanalyses, future trialists should try to collect data in such a way as to be compatible with the basic outcome assessments reviewed here (eg early death, fatal intracranial haemorrhage, poor functional outcome).

The third international stroke trial (IST-3) main results: primary and secondary outcomes among 3035 patients

The IST3 collaborative group - 156 hospitals in UK, Poland, Italy, Sweden, Norway, Australia, Portugal, Belgium, Austria, Switzerland, Canada, Mexico

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The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial

*The IST-3 collaborative group**

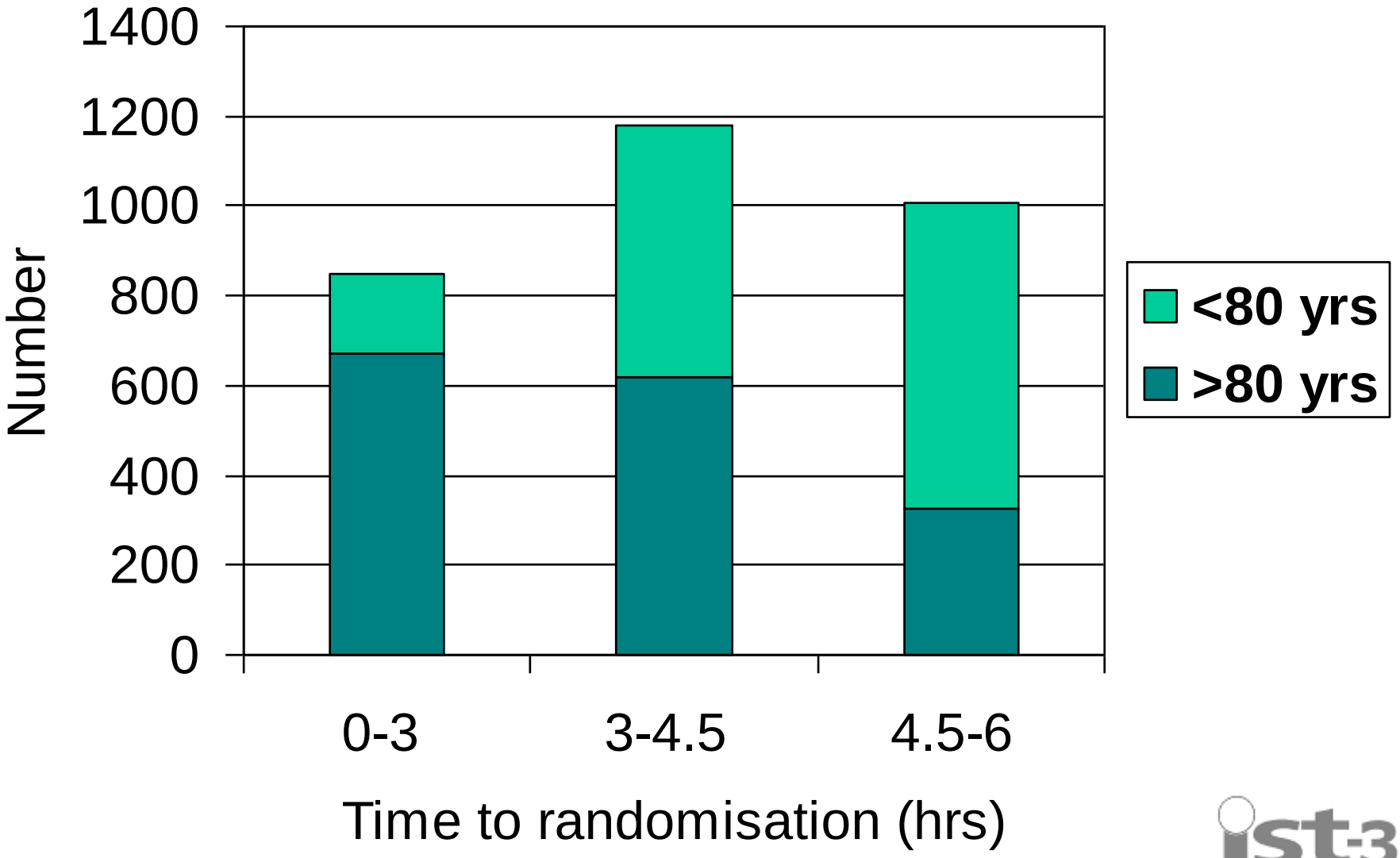
Baseline characteristics[1] (n=3035)

- 849 (28%) randomised < 3 hours
- 1617 (53%) aged > 80 years
- 970 (32%) baseline NIHSS ≥ 16
- 95% did not meet EU approval for rt-PA
- Treatment and control groups balanced on all key factors

1.Trials 2011, 12:252. http://www.trialsjournal.com/content/12/1/252

IST-3 Thrombolysis

Time to randomisation and age



Fatal & non-fatal intracranial haemorrhage < 7 days

rt-PA (n=1515)		Control (n=1520)	
n	(%)	n	(%)
104	(7%)	16	(1%)

P < 0.0001

applying the 'Cochrane' definition, of SICH, the 7% IST-3 frequency is comparable with the 7.3% (SITS) registry of 6483 patients treated within licence in routine clinical practice[1]

1. Wahlgren, Lancet 2007; 369: 275–82

ist-3 Thrombolysis

Deaths

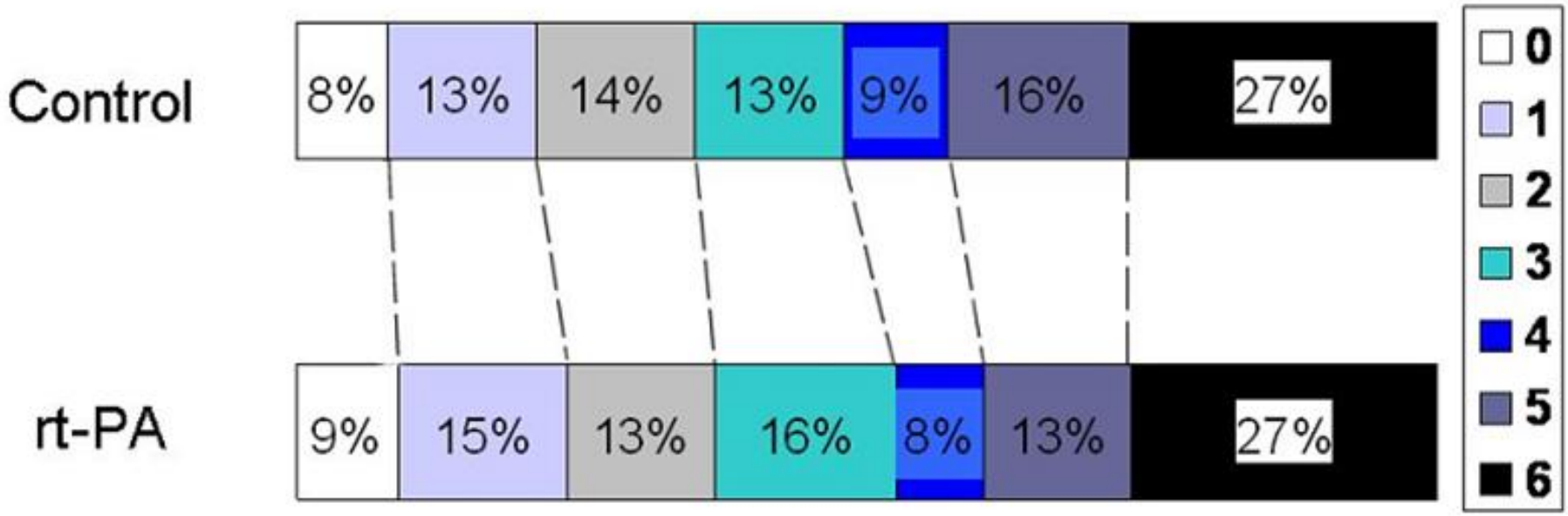
	rt-PA n	rt-PA (%)	Control n	Control (%)	p
Within 7 days	163	(11%)	107	(7%)	↑0.001
After 7 days, before 6 mo.	244	(16%)	300	(20%)	↓0.009
All deaths by 6 months.	408	(27%)	407	(27%)	0.6

Overall - all patients 0-6 hrs: ‘alive and independent’ (OHS 0-2)

rt-PA (n=1515)		control (n=1520)	
n	(%)	n	(%)
554	(37%)	534	(35%)

Absolute difference/1000
= 14 more alive and independent
(95% CI -20 to 48) **NS**

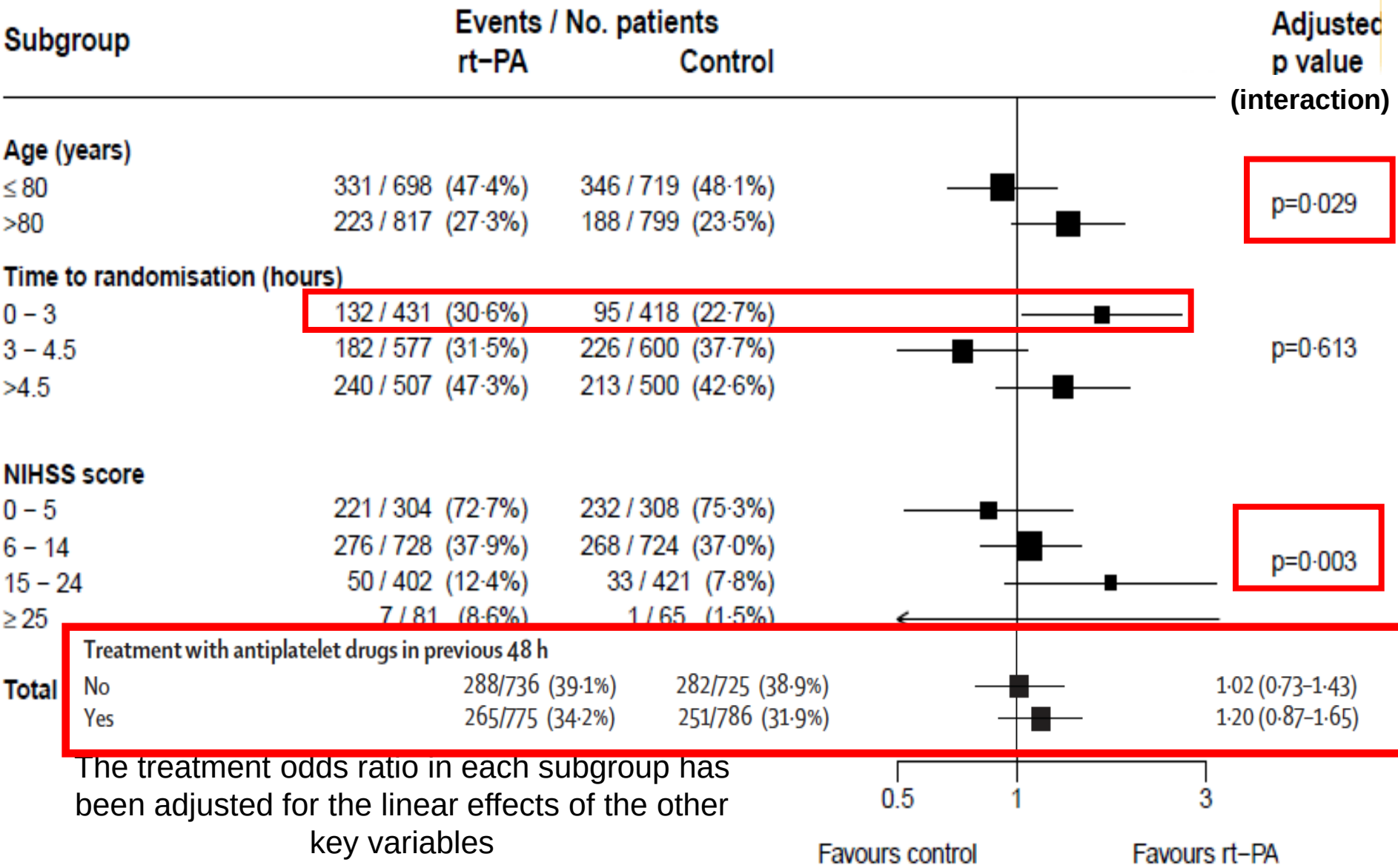
Ordinal analysis 6 month OHS



Favourable shift; adjusted common odds ratio 1·27 (95% CI 1·10- 1·47), p=0·001
or, the odds of surviving with less disability were 27% greater for patients treated with rt-PA

ist-3 Thrombolysis

Subgroups: adjusted effect on primary outcome



The treatment odds ratio in each subgroup has been adjusted for the linear effects of the other key variables

Implications for practice. IST-3 enables clinicians to:

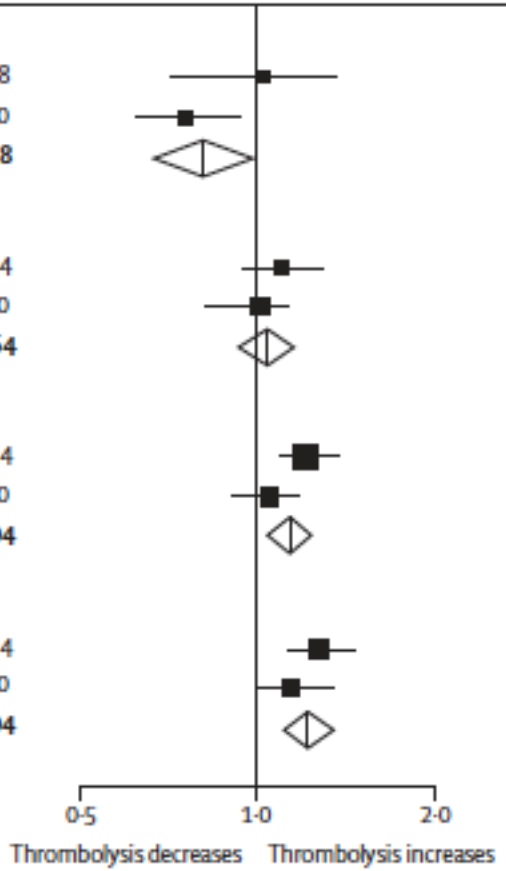
- Consider thrombolytic treatment for a wider variety of patients,
  - Particularly those **aged over 80 years**
  - With **more severe strokes**
- Reinforce their efforts to increase the proportion of ischaemic strokes **treated < 3 hours**
- Have greater confidence that **mortality is not increased by treatment**

ist-3 Thrombolysis

Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis

Joanna M Wardlaw, Veronica Murray, Eivind Berge, Gregory del Zoppo, Peter Sandercock, Richard L Lindley, Geoff Cohen

	Trials	Events/patients		Odds ratio (95% CI)	Heterogeneity
		rt-PA	Control		
All deaths between 7 days and final follow-up					
All trials before IST-3	7	78/1292	72/1208	1·04 (0·75–1·45)	χ^2_1=2·11 (p=0·1)
IST-3	1	245/1515	300/1520	0·79 (0·65–0·95)	
All trials	**8**	**323/2807**	**372/2728**	**0·84 (0·71–0·99) p=0·03**	
All deaths					
All trials before IST-3	11	271/2033	233/1944	1·14 (0·95–1·38)	χ^2_1=1·00 (p=0·3)
IST-3	1	408/1515	407/1520	1·01 (0·86–1·18)	
All trials	**12**	**679/3548**	**640/3464**	**1·06 (0·94–1·20) p=0·33**	
Alive and independent (mRS 0–2)					
All trials before IST-3	9	1057/1968	900/1884	1·27 (1·12–1·45)	χ^2_1=3·08 (p=0·08)
IST-3	1	554/1515	534/1520	1·06 (0·92–1·23)	
All trials	**10**	**1611/3483**	**1434/3404**	**1·17 (1·06–1·29) p=0·001**	
Favourable outcome (mRS 0–1)					
All trials before IST-3	9	848/1968	678/1884	1·35 (1·19–1·55)	χ^2_1=1·18 (p=0·3)
IST-3	1	363/1515	320/1520	1·18 (1·00–1·40)	
All trials	**10**	**1211/3483**	**998/3404**	**1·29 (1·16–1·43) p<0·0001**	



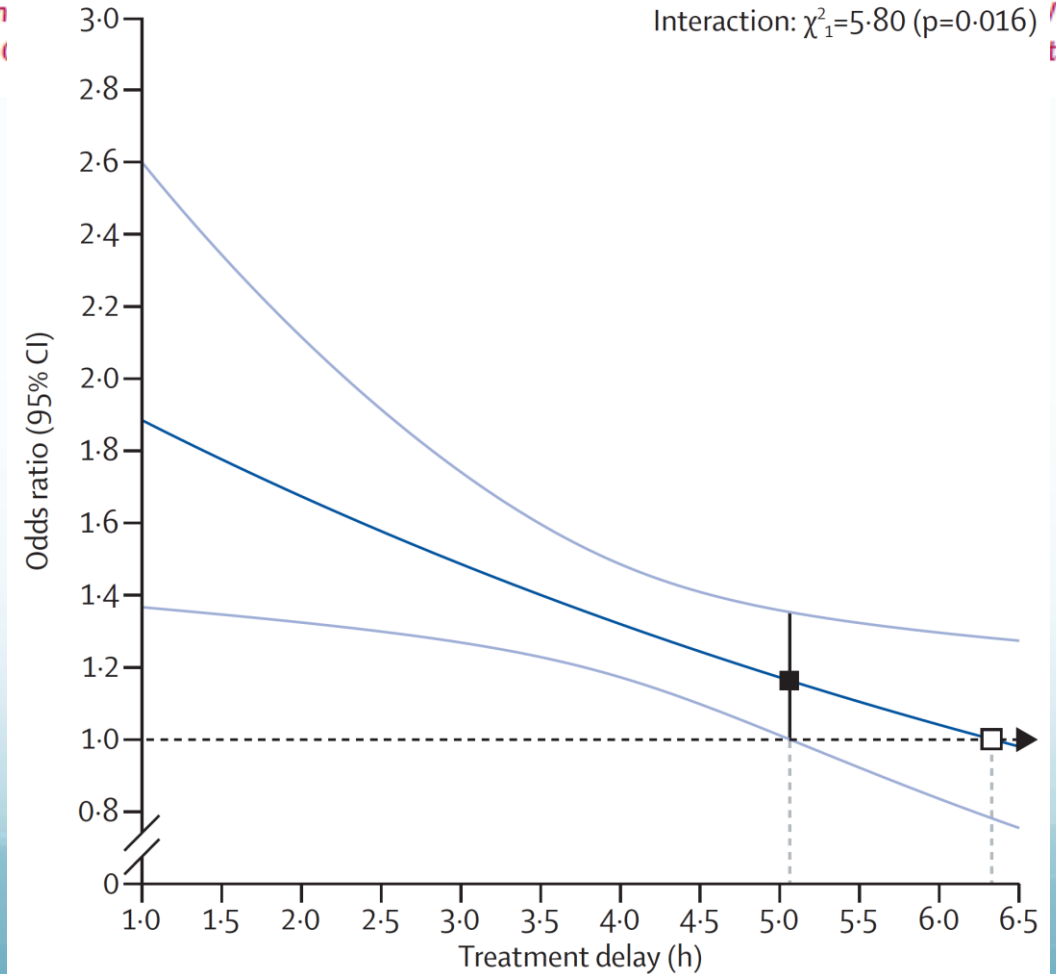
should proceed as fast as possible

IST-3 Thrombolysis

Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials

Magnitude of the IV tPA response by treatment delay

Jonathan Emberson*, Kennedy R Lees*, Patrick Lyden*, Lisa Blackwell, Gregory Albers, Erich Bluhmki, Thomas Brott, Geoff Cohen, Stephen Davis, Geoffrey Donnan, James Grotta, George Howard, Markku Kaste, Masatoshi Koga, Ruediger von Kummer, Maarten Lansberg, Richard I Lindley, Gordon Murray, Jean ... ardlaw, William Whiteley, Gregory J del Zoppo, ... tive Group



Emberson Lancet 2014

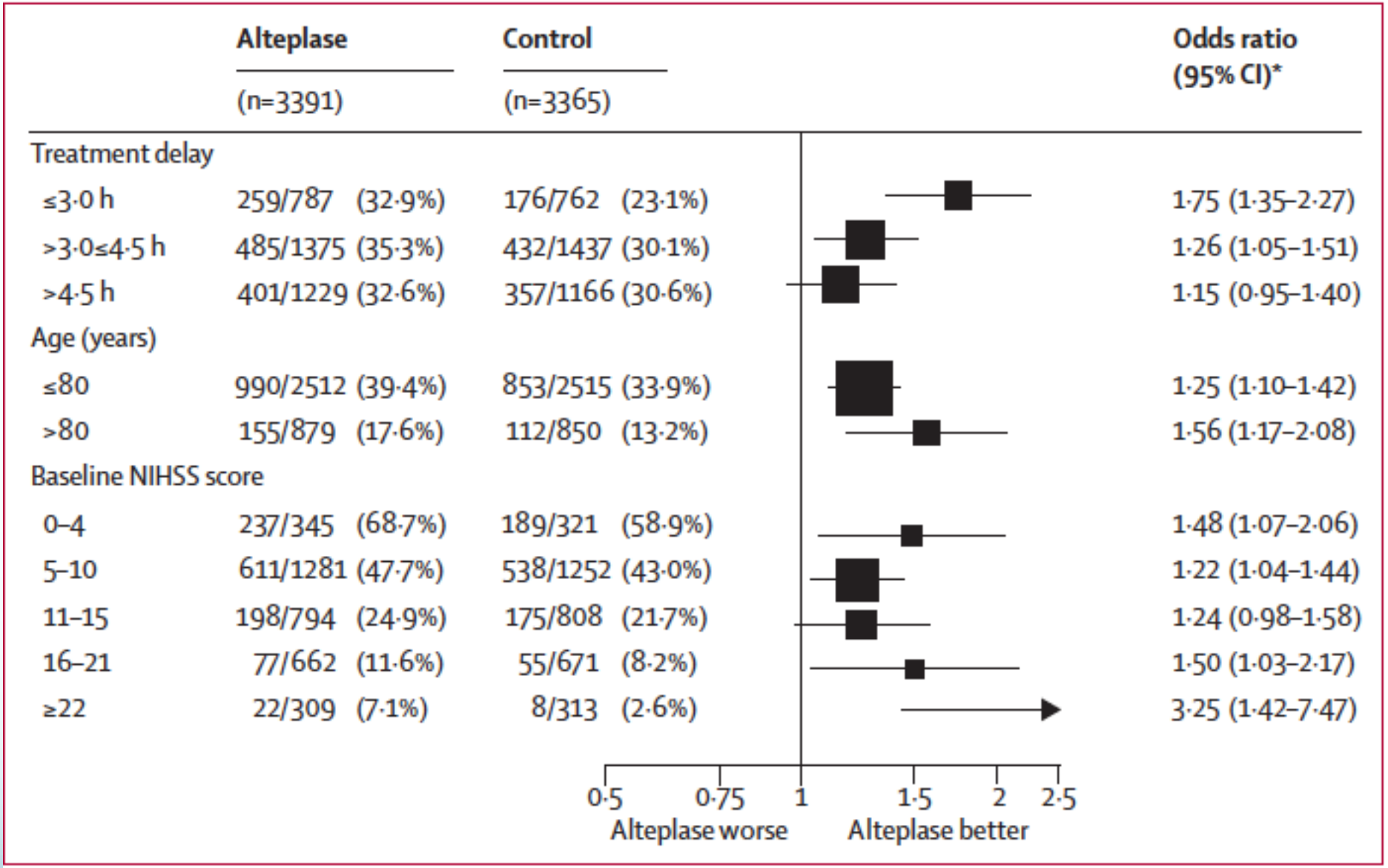
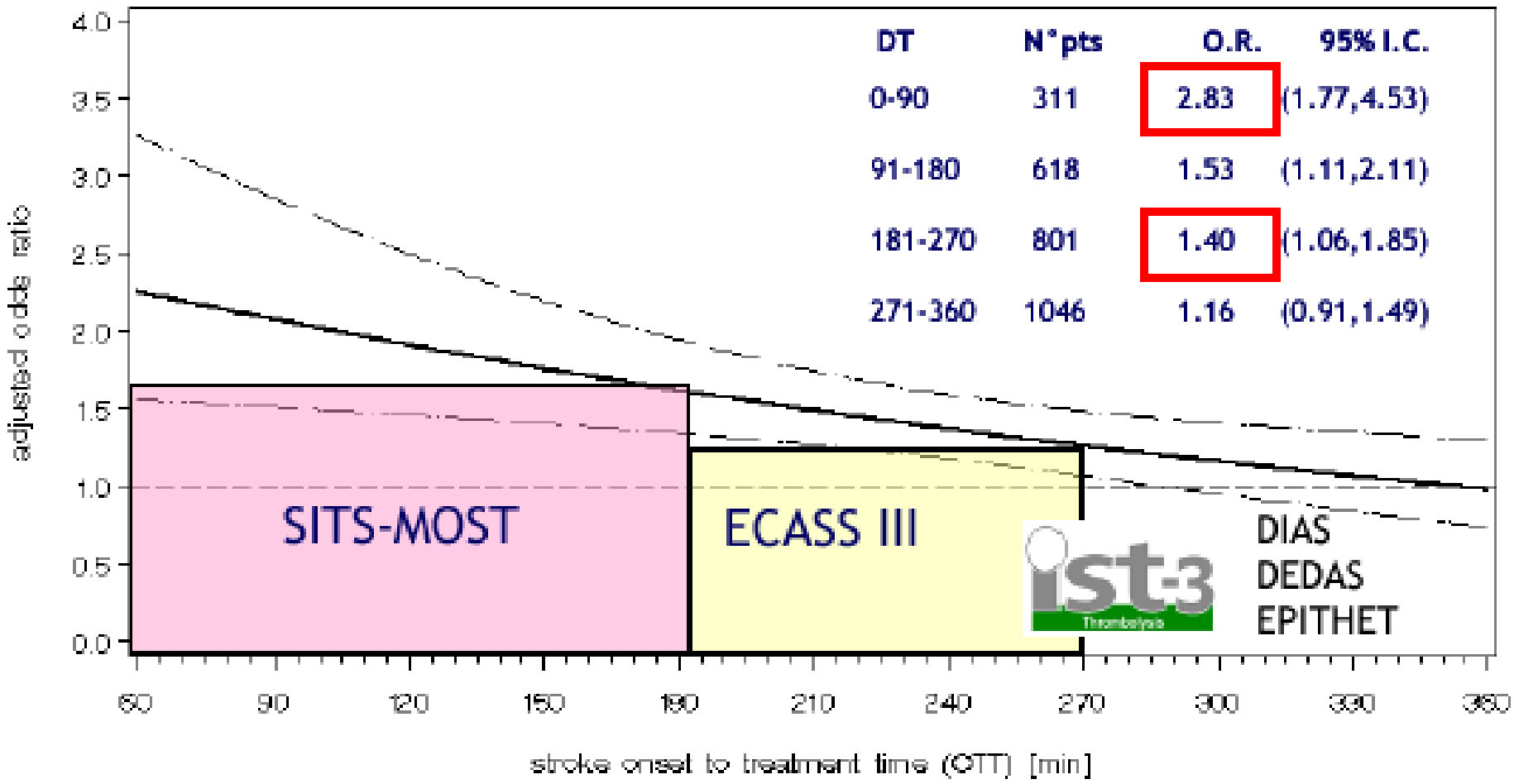


Figure 2: **Effect of alteplase on good stroke outcome (mRS 0–1), by treatment delay, age, and stroke severity**

Emberson Lancet 2014

Lancet 2004; 363: 768-74



Criteri di inclusione
Trombolisi ev

1. **Pazienti di ambo i sessi di età compresa tra >18 anni**
2. **Ictus ischemico responsabile di un deficit misurabile di linguaggio, moto, sguardo, campo visivo e neglect (esclusione TC di emorragia) No limite inferiore definito**
3. **Trattamento entro le 4.5 ore dall'esordio**
4. **Sintomi presenti da almeno 30 min e non in rapido e significativo miglioramento *(per escludere TIA).***
5. **Consenso informato scritto del paziente o del familiare al trattamento e trattamento dei dati**

Grazie per l’attenzione