

ischemic stroke

recent observations of thrombosis and hemostasis in the CNS

NATF
boston, 26 september, 2009

Gregory J. del Zoppo, M.D.
Department of Medicine (/Hematology)
Department of Neurology
University of Washington
Seattle, Washington

topics

- acute plasminogen activator intervention: ECASS-III and extension of the 3-hour window
- secondary prevention following ischemic stroke
- nonvascular plasminogen activator participation in cerebral ischemia

etiology of focal cerebral ischemia

source	frequency
<u>ischemic stroke</u>	
atherothrombotic events	40 – 57%
thromboembolism	16 – 23%
lacunae	14%
<u>hemorrhagic stroke</u>	
intracerebral hemorrhage	4 – 18%
subarachnoid hemorrhage	10 – 19%

treatment approaches

1. neuroprotectant

target: neurons

approaches:

Ca²⁺ channel regulation

neurotransmitters

cell demise pathways

2. anti-thrombotic agents

target: vascular-dependent processes

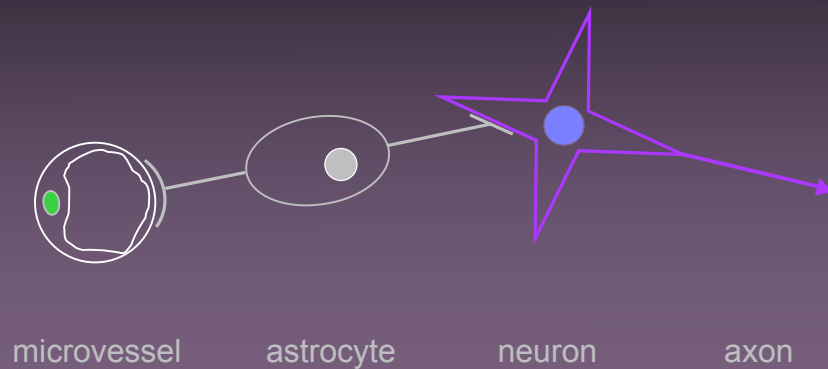
approaches:

plasminogen activators

anticoagulation

anti-platelet agents

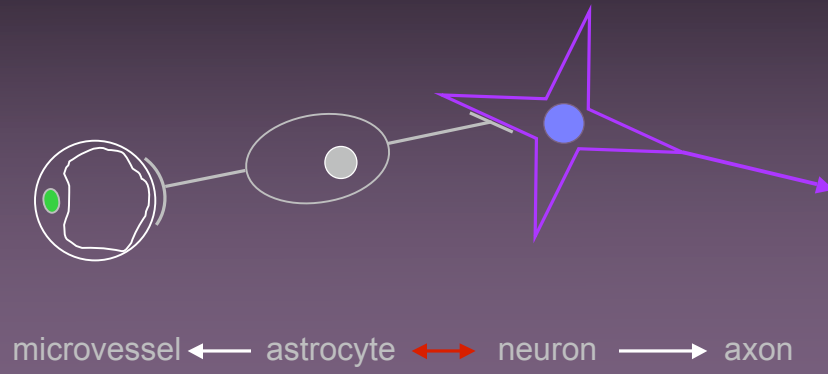
targets of injury



the “neurovascular unit”

- conceptual framework which links microvessel and neuron function, and their responses to injury
- structural arrangement which links microvessel components with neurons via common astrocytes

the “neurovascular unit”



acute plasminogen activator intervention

unresolved issues

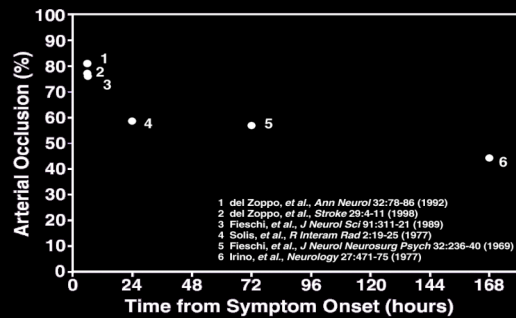
- patient selection
- maximizing acute intervention
- hemostasis within the ischemic territory
- mechanisms of hemorrhage
- minimizing hemorrhagic risk
- neuron protection
- interaction of microvessels and neurons:
the neurovascular unit

unresolved issues

- patient selection
- maximizing acute intervention
- hemostasis within the ischemic territory
- mechanisms of hemorrhage
- minimizing hemorrhagic risk
- neuron protection
- interaction of microvessels and neurons:
the neurovascular unit

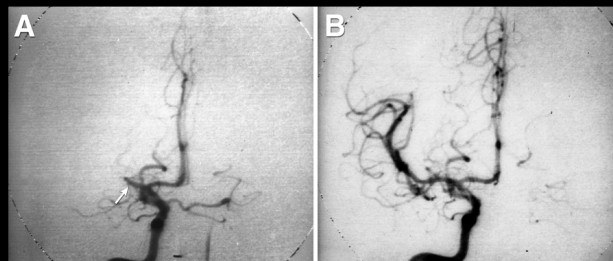
recent events

- clinical trials
 - ECASS-3
 - ancrod
 - rt-PA + integrilin
- strategies to limit the impact of PH following thrombus lysis
- the normal participation of plasminogen in the NVU to maintain communication, and respond to focal ischemia
- patient selection (use of perfusion/diffusion characteristics)



carotid territory
ischemic stroke

del zoppo gj *et al* stroke 19:
307-313 (1988)

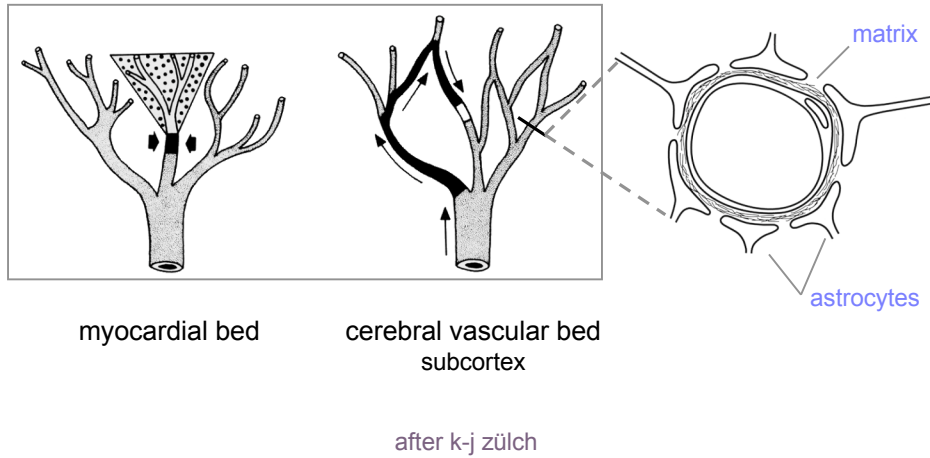


A 3 hr post-symptom onset

B 1 hr after local u-PA

intrinsic collateral protection

myocardial and cerebral microvascular beds



anti-thrombotic intervention

phase III trials of plasminogen activators

NINDS-sponsored acute stroke trial

ECASS

ECASS-II

ECASS-III

PROACT

PROACT-2

anti-thrombotic intervention
positive phase III trials of plasminogen
activators

NINDS-sponsored acute stroke trial

ECASS

ECASS-II

ECASS-III

PROACT

PROACT-2

anti-thrombotic intervention
neutral phase III trials of plasminogen
activators

NINDS-sponsored acute stroke trial

ECASS

ECASS-II

ECASS-III

PROACT

PROACT-2

death or dependency

modified Rankin scale

IV SK vs. control

IV rt-PA vs. control

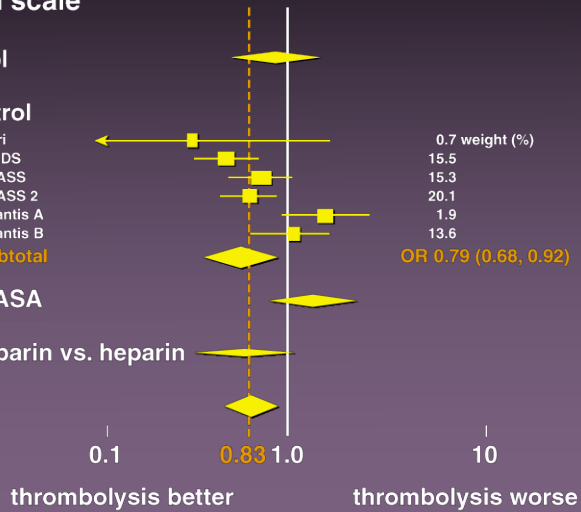
Mori
NINDS
ECASS
ECASS 2
Atlantis A
Atlantis B
subtotal

IV SK+ASA vs. ASA

IA rscu-PA + heparin vs. heparin

TOTAL

12 trials
4476 patients



plasminogen activators in acute thrombotic stroke

study	agent	$\Delta(t-o)$ (hr)	n	recanalization %	hemorrhage %
<i>carotid territory: intra-arterial delivery*</i>					
del Zoppo <i>et al</i>	SK/u-PA	1-24	20	90.0	20.0
Mori <i>et al</i>	u-PA	<7	22	45.5	18.2
Matsumoto <i>et al</i>	u-PA	1-24	40	60.0	32.5
<i>carotid territory: intravenous delivery**</i>					
Yamaguchi <i>et al</i>	rt-PA	<6	52	38.5	28.6
von Kummer <i>et al</i>	rt-PA	<6	22	59.1	36.4
del Zoppo <i>et al</i>	rt-PA	<8	93 (104)	34.4	30.8
Mori <i>et al</i>	rt-PA	<6	19	47.4	52.6
	C		12	16.7	41.7
Yamaguchi <i>et al</i>	rt-PA	<6	47 (51)	21.3	47.1
	C		46 (47)	4.4	46.8

* 1988-90

** 1990-93

rt-PA in acute ischemic stroke

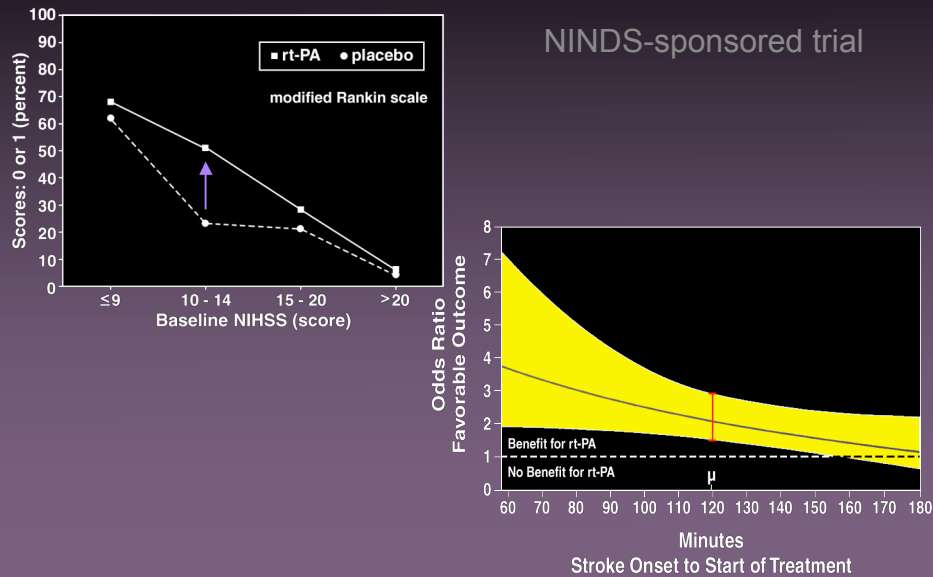
study	agent	n	$\Delta(t-o)$	dose
NINDS	rt-PA	312	3.0 hr	0.9 mg/kg
	C	312		
ECASS	rt-PA	313	6.0 hr	1.1 mg/kg
	C	307		
ECASS II	rt-PA	409	6.0 hr	0.9 mg/kg
	C	391		

NINDS new engl j med 333:1581-1587 (1995)
 hacke w *et al*, JAMA 274:1017-1025 (1995)
 hacke w *et al*, lancet 352:1245-1251 (1998)

rt-PA in acute ischemic stroke prescribed analysis

study	agent	outcome		
		modified Rankin	benefit	Δ
NINDS	rt-PA	0 - 1	39%	13%*
	C		26%	
ECASS	rt-PA	median	3	0
	C		3	
ECASS II	rt-PA	0 - 1	40.4%	3.8%
	C		36.6%	

conditions of beneficial outcome



licensure of rt-PA for ischemic stroke Europe

1. provisional approval for < 3.0 hours based on NINDS data
2. EMEA-required registry of patient treatment
SITS-MOST
SITS-ISTR
3. EMEA-required successful performance of prospective double blinded placebo-controlled trial in 3.0 - 4.0 (4.5)-hour window
4. basis for approval for the < 3.0 -hour window

rt-PA in acute ischemic stroke

study	agent	n	$\Delta(t-o)$	dose
NINDS	rt-PA	312	3.0 hr	0.9 mg/kg
	C	312		
ECASS	rt-PA	313	6.0 hr	1.1 mg/kg
	C	307		
ECASS II	rt-PA	409	6.0 hr	0.9 mg/kg
	C	391		
ECASS III	rt-PA	418	3.0 - 4.5 hr	0.9 mg/kg
	C	403		

hacke w *et al* new engl j med 359: 1317-1328 (2008)

ECASS III

aim: randomized trial to be conducted in which “therapeutic window” was extended beyond 3 hours

design: prospective randomized double blinded placebo-controlled trial, 3.0 – 4.5 hours from symptom onset

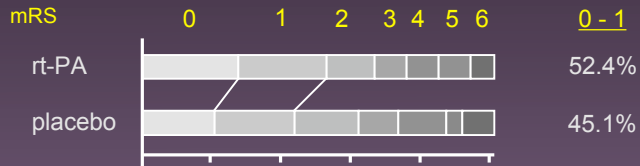
primary outcome: disability (mRS = 0 –1) at 90 days

secondary outcome: global outcome measure

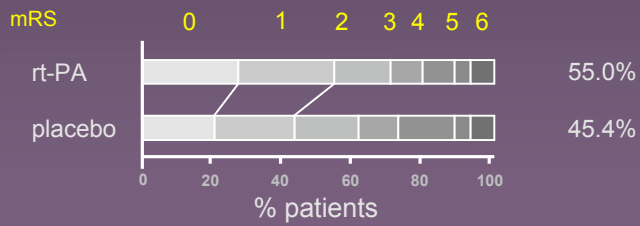
safety outcomes: overall mortality at 90 days, any intracranial hemorrhage, symptomatic intracranial hemorrhage, symptomatic edema

ECASS III

intention-to-treat population



per-protocol population



ECASS III

hemorrhagic transformation

adverse events	rt-PA n = 416		placebo n = 403		OR	<i>p</i>
any ICH	113	27.0	71	17.6	1.73	0.001
symptomatic ICH	-	-	-	-	-	-
ECASS III definition	10	2.4	1	0.2	9.85	0.008
ECASS II definition	22	5.3	9	2.2	2.43	0.02
SITS-MOST definition	8	1.9	1	0.2	7.84	0.02
NINDS definition	33	7.9	14	3.5	2.38	0.006

rt-PA in acute ischemic stroke prescribed analysis

study	agent	outcome		
		modified Rankin	benefit	Δ
NINDS	rt-PA	0 - 1	39%	13%*
	C		26%	
ECASS	rt-PA	median	3	0
	C		3	
ECASS II	rt-PA	0 - 1	40.4%	3.8%
	C		36.6%	
ECASS III	rt-PA	0 - 1	52.4%	7.2%*
	C		45.2%	

rt-PA in acute ischemic stroke hemorrhagic transformation

study	agent	hemorrhage			
		nil	HI	PH	(%)
NINDS	rt-PA	278	14	20	(6.4)*
	C	301	9	2	(0.6)
ECASS	rt-PA	179	72	62	(19.8)*
	C	184	93	30	(6.5)
ECASS II	rt-PA	219	142	48	(11.7)*
	C	238	141	12	(3.1)
ECASS III	rt-PA			22	(5.3)* +
	C			9	(2.2)

ECASS III

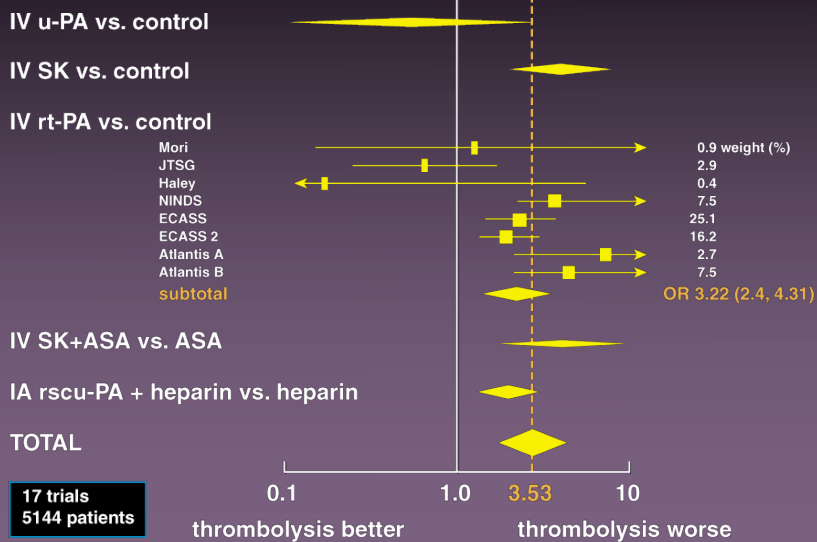
additional

exclusion criteria

- patients older than 80 years
- patients taking oral anticoagulants with an INR ≤ 1.7
- baseline NIHSS score ≥ 25
- patients with a history of stroke and diabetes

hacke w *et al* new engl j med 359: 1317-1329 (2008)
del zoppo gj *et al* stroke 40: 2945-2948 (2009)

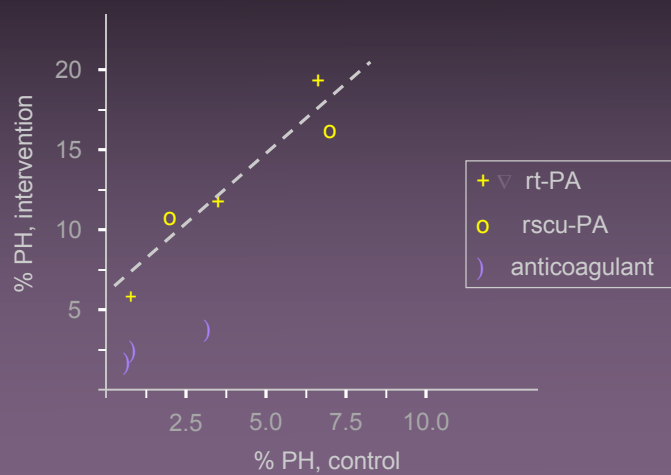
symptomatic hemorrhage



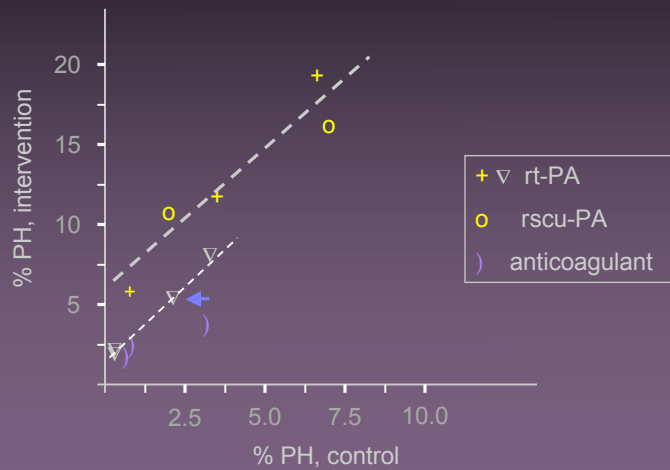
hemorrhagic transformation

factors	agent
time from symptom onset	rt-PA (d)
diastolic hypertension	rt-PA
low body mass	rt-PA
age	rt-PA
atrial fibrillation	rt-PA
“early signs” of Ischemia	rt-PA rscu-PA
rt-PA	rt-PA

hemorrhagic risk depends on patient population



hemorrhagic risk depends on patient population and definition



risk of hemorrhage

dependent upon

- the time from the onset of ischemia
- the depth of ischemic injury
- patient population
- definition of hemorrhage

studies with plasminogen activators

study	agent	type	outcome
ECASS-3	rt-PA	phase III	benefit/safety
DIAS	rDS-PA	phase I	dose-finding safety
DEDAS	rDS-PA	phase II	dose-finding safety (MR)
DIAS-2	rDS-PA	phase III	benefit/safety
DIAS-3	rDS-PA	phase III	benefit/safety
DEFUSE	rt-PA	phase III	benefit/safety (MR)
DEFUSE-2	rt-PA	phase III	benefit/safety (MR)
	TNK	phase III	benefit/safety

reperfusion desmoteplase, rDS-PA

DIAS

hacke w *et al* stroke 36: 66-73 (2005)

phase II blinded placebo dose-finding efficacy trial

n = 104 in two parts (part 1 = 47; part 2 = 57)

treatment 3-9 hr MR PWI/DWI mismatch

part 1 37.5/50 mg rDS-PA (n = 13)**

25 mg rDS-PA (n = 17)

placebo (n = 16)

part 2 62.5 µg/kg rDS-PA (n = 15)

90 µg/kg rDS-PA (n = 15)

125 µg/kg rDS-PA (n = 15)

placebo (n = 11)

primary outcome: symptomatic ICH

co-primary outcomes: reperfusion, NIHSS 0 or 1, $\Delta >$

reperfusion desmoteplase, rDS-PA

DIAS			hemorrhage		recanalization	
	dose	n				
part 1	37.5/50 mg	13	4	30.8	6	46.2*
	25 mg	17	4	23.5	9	56.3*
	placebo	16	0	0.0	3	18.8
part 2	62.5 µg/kg	15	0	0.0	3	23.1
	90 µg/kg	15	1	6.7	7	46.7*
	125 µg/kg	15	0	0.0	10	71.4* **
	placebo	11	0	0.0	2	20.0

reperfusion desmoteplase, rDS-PA

DEDAS

furlan aj *et al* stroke 37: 1227-1231 (2006)

phase II blinded placebo dose-finding efficacy trial
n = 37

treatment 3-9 hr MR PWI/DWI mismatch

90 µg/kg rDS-PA (n = 14)

125 µg/kg rDS-PA (n = 15)

placebo (n = 8)

primary outcome: symptomatic ICH

co-

primary outcomes:

reperfusion at 4-8 hr

NIHSS 0 or 1, mRS 0-2, BI 75-100 at 90 days

*prior to unblinding, MR target population defined

reperfusion desmoteplase, rDS-PA

DEDAS		n	hemorrhage		recanalization		outcome	
	dose							
ITT	90 µg/kg	14	0	0.0	2	18.2	4	28.6
	125 µg/kg	15	0	0.0	8	53.3	9	60.0
	placebo	8	0	0.0	3	37.5	2	25.0

reperfusion desmoteplase, rDS-PA

DEDAS		n	hemorrhage		recanalization		outcome	
	dose							
ITT	90 µg/kg	14	0	0.0	2	18.2	4	28.6
	125 µg/kg	15	0	0.0	8	53.3	9	60.0
	placebo	8	0	0.0	3	37.5	2	25.0

target population: improvement in 90 d "good outcome" with 125 µg/kg dose ($p = 0.022$)

reperfusion desmoteplase, rDS-PA

DIAS-2

PAION/Forest press release (31 may, 2007)

phase III blinded placebo-controlled efficacy trial with
dose-finding efficacy trial

n = 186 in two groups

treatment 3-9 hr, rt-PA allowed

90 µg/kg rDS-PA (n = 57)

125 µg/kg rDS-PA (n = 66)

placebo (n = 57)

primary

outcome: difference between rDS-PA and
placebo in per cent composite responders.

no efficacy compared to placebo

reperfusion desmoteplase, rDS-PA

DIAS-3

Lundbeck

phase III blinded placebo-controlled efficacy trial with
dose-finding efficacy trial

CTA instead of MR

studies with plasminogen activators

study	agent	type	outcome
ECASS-3	rt-PA	phase III	benefit/safety
DIAS	rDS-PA	phase I	dose-finding safety
DEDAS	rDS-PA	phase II	dose-finding safety (MR)
DIAS-2	rDS-PA	phase III	benefit/safety
DIAS-3	rDS-PA	phase III	benefit/safety
DEFUSE	rt-PA	phase III	benefit/safety (MR)
DEFUSE-2	rt-PA	phase III	benefit/safety (MR)
	TNK	phase III	benefit/safety

potential role of perfusion defect and territory of focal injury (diffusion)

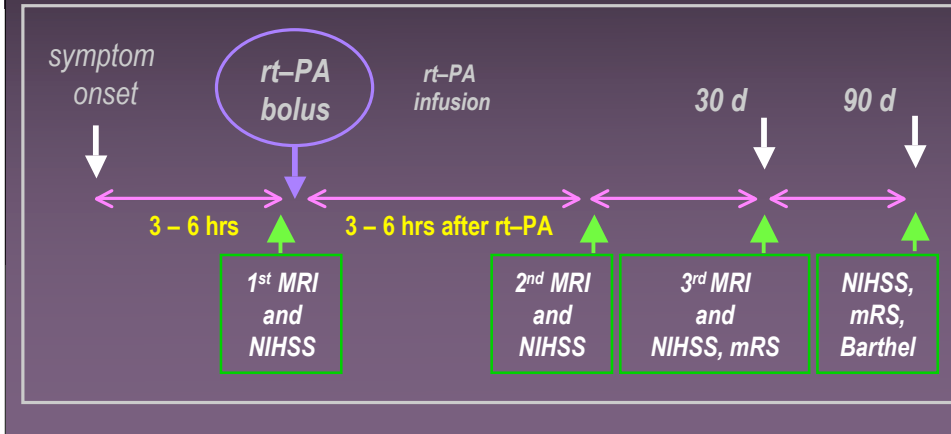
Magnetic Resonance Imaging Profiles Predict Clinical Response to Early Reperfusion: The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study

Gregory W. Albers, MD,¹ Vincent N. Thijs, MD, PhD,³ Lawrence Wechsler, MD,⁴ Stephanie Kemp, BS,¹ Gottfried Schlaug, MD, PhD,⁵ Elaine Skalabrin, MD,⁶ Roland Bammer, PhD,² Wataru Kakuda, MD,¹ Maarten G. Lansberg, MD, PhD,¹ Ashfaq Shuaib, MD,⁷ William Coplin, MD,⁷ Scott Hamilton, PhD,¹ Michael Moseley, PhD,² and Michael P. Marks, MD,² for the DEFUSE Investigators

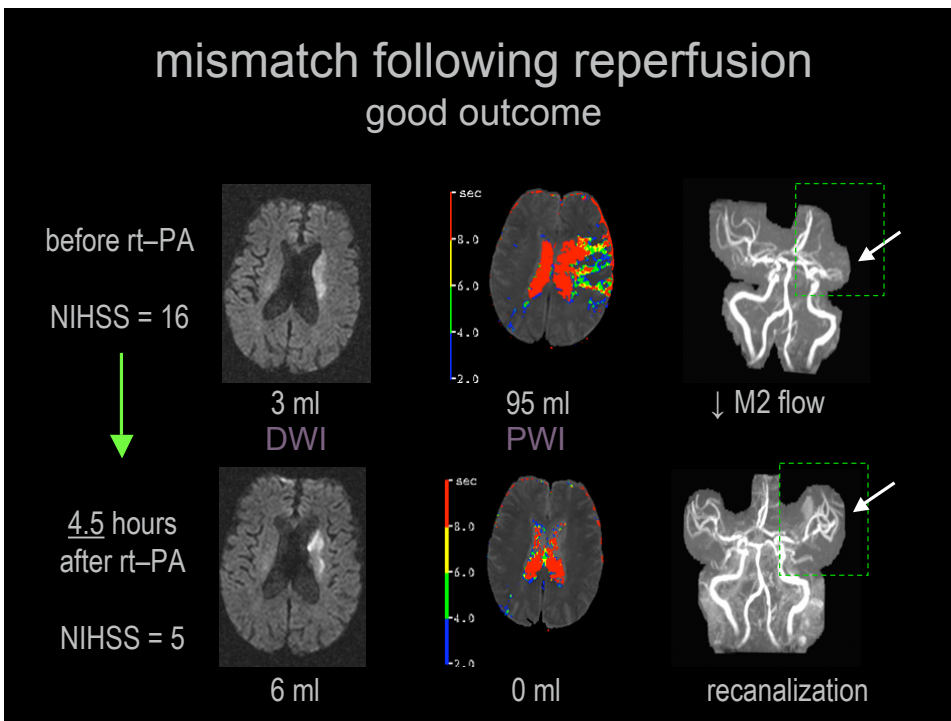
ann neurology 60: 508-517 (2006)

DEFUSE

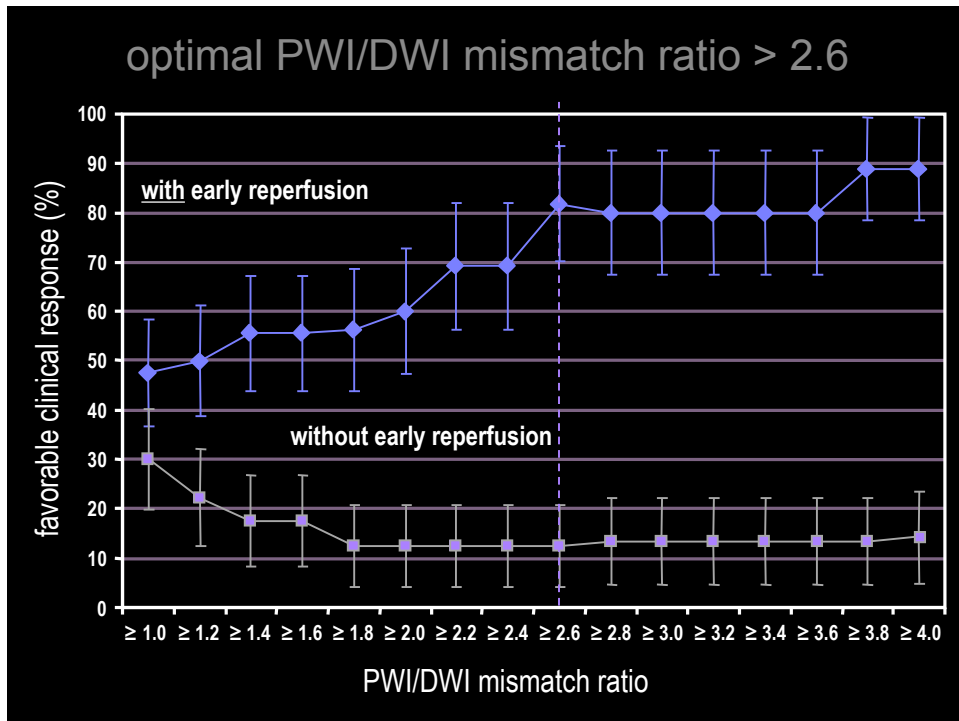
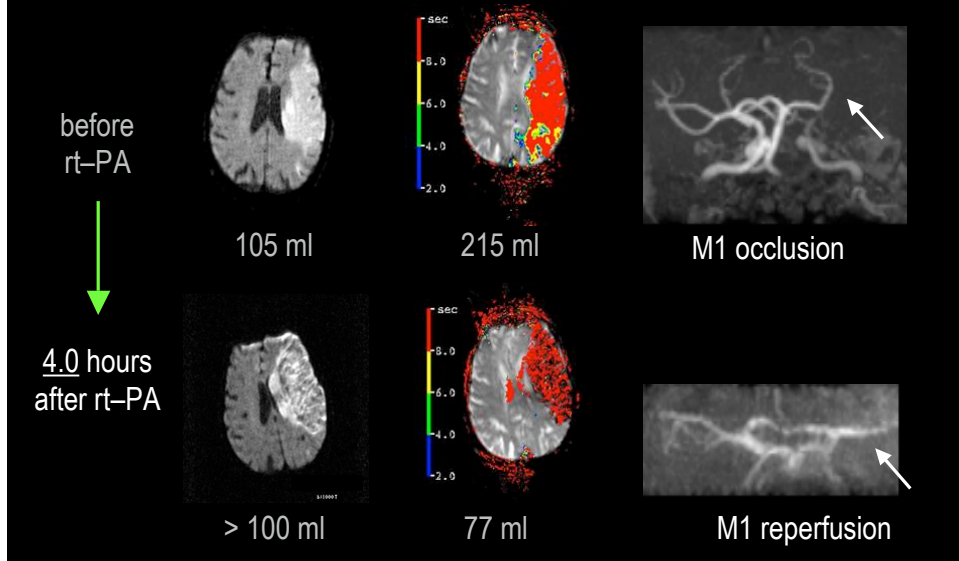
- prospective pilot study (n = 74)
- identify MRI patterns (of PWI and DWI) that describe the clinical response to early reperfusion



mismatch following reperfusion good outcome



mismatch following reperfusion "malignant mismatch"



summary

- small lesions have a uniformly favorable outcome
- PWI/DWI mismatch ratio > 2.6 appropriate threshold (conventional ratio threshold > 1.2)
- large DWI lesion volume and early reperfusion associated with symptomatic hemorrhagic transformation (ICH)
- refining characteristics of patients with favorable clinical outcome following early recanalization within 6-hour time window

ancrod (ASP-I and ASP-II)

studies with plasminogen activators

study	agent	type	outcome
ECASS-3	rt-PA	phase III	benefit/safety
DIAS	rDS-PA	phase I	dose-finding safety
DEDAS	rDS-PA	phase II	dose-finding safety (MR)
DIAS-2	rDS-PA	phase III	benefit/safety
DIAS-3	rDS-PA	phase III	benefit/safety
DEFUSE	rt-PA	phase III	benefit/safety (MR)
DEFUSE II	rt-PA	phase III	benefit/safety (MR)
CLEAR	rt-PA +	phase II/III	benefit/safety

secondary prevention

European Stroke Prevention Study 2 (ESPS 2)

Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)

European Stroke Prevention Study 2 (ESPS 2)

aim: compare the relative efficacy and safety of ASA (25 mg), ERDP (200 mg), ASA + ERDP, or placebo among 6,000 patients with recent ischemic stroke

design: multicenter, randomized, double-blind, placebo-controlled with a 2 x 2 factorial distribution

primary outcome: fatal/non-fatal stroke, any cause mortality, stroke and/or mortality

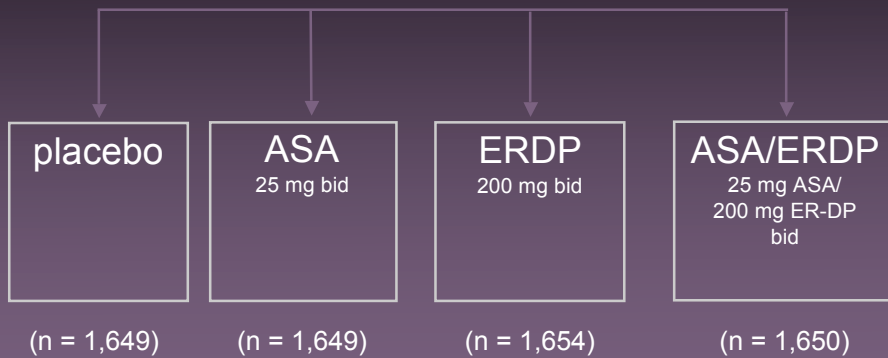
secondary outcome: TIA, MI, vascular events (APT definition), other vascular events

safety outcomes: major/minor hemorrhagic events, intracerebral hemorrhage

ESPS 2 group. *J Neurol Sci* 151:S1-S77 (1997)

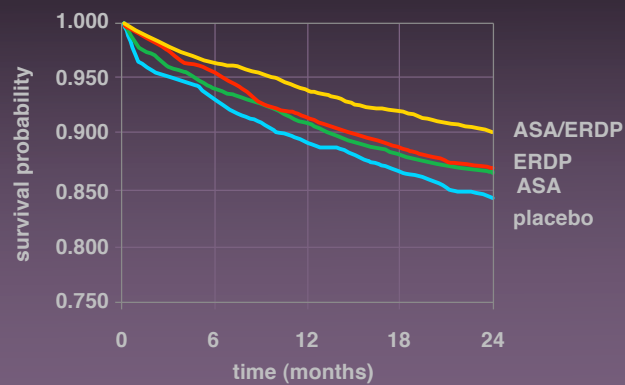
ESPS 2

n = 6,602



ESPS 2 group. *j neurol sci* 151:S1-S77 (1997)

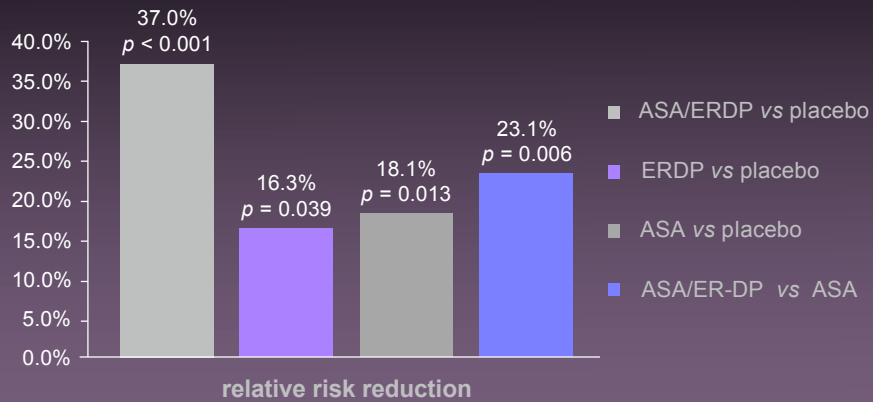
ESPS 2 stroke survival



all patients

diener hc *et al j neurol sci* 143:1-13 (1996)

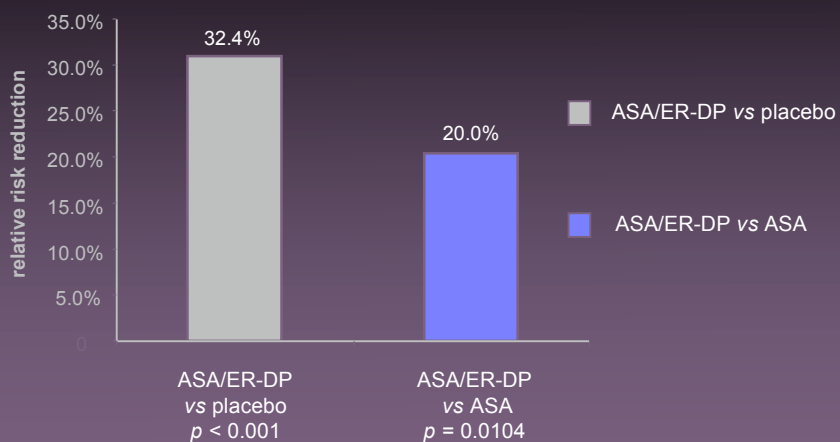
ESPS 2 effects on stroke



pairwise comparisons

ESPS 2 group. j neurol sci 151:S1-S77 (1997)

ESPS 2: secondary outcome stroke, MI, vascular death

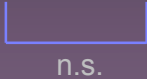


ESPS 2: adverse events

treatment group	dyspepsia	GI hem	headache	
ASA/ERDP	18.4	4.1*	39.2	%
placebo	16.7	2.1	32.9	
ASA	18.1	3.2	33.8	
ERDP	17.4	2.2	38.3	

* not statistically different from aspirin

ESPS 2: safety severe or fatal hemorrhage

placebo	ERDP	ASA	ERDP + ASA
7	6	20	27
(0.4%)	(0.4%)	(1.2%)	(1.6%)
		 n.s.	

ESPS 2 group. j neurol sci 151:S1-S77 (1997)

Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS)

aim: compare the relative efficacy and safety of ASA/ERDP with clopidogrel among patients with recent ischemic stroke

design: prospective 2 x 2 factorial randomized blinded placebo controlled trial

ASA (20 mg)/ERDP (200 mg) clopidogrel 75 mg daily

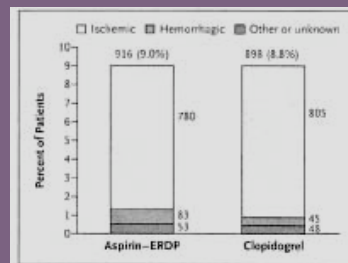
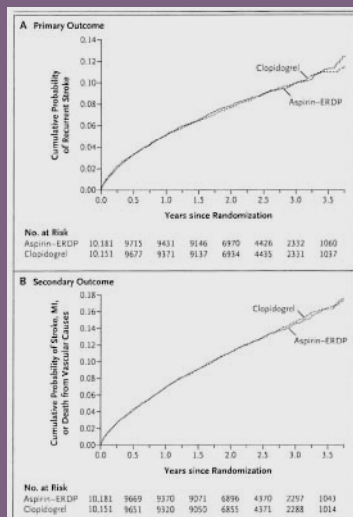
primary outcome: recurrent stroke of any type

secondary outcome: composite of stroke, MI, mortality

safety outcomes: major/minor hemorrhagic events, intracerebral hemorrhage

sacco rl *et al* new engl j med 359: 1238-1251 (2008)

Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS)



sacco rl *et al* new engl j med 359: 1238-1251 (2008)

Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS)

	ASA/ERDP		clopidogrel		HR
primary outcome	916	9.0	898	8.8	1.01 (0.92-1.11)
secondary outcome	1333	13.1	1333	13.1	0.99 (0.92-1.07)
tertiary outcome					
first ischemic stroke	789	7.7	807	7.9	0.97 (0.88-1.07)
major hemorrhage	419	4.1	365	3.6	1.15 (1.00-1.32)
minor/major hemorrhage	535	5.3	494	4.9	1.08 (0.96-1.22)
ICH	90	0.9	55	0.5	1.42 (1.11-1.83)*
fatal	28	0.3	29	0.3	
nonfatal	62	0.6	26	0.3	

Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS)

“The trial did not meet the predefined criteria for noninferiority but showed similar rates of recurrent stroke with ASA-ERDP and with clopidogrel. There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke.”

sacco rl *et al* new engl j med 359: 1238-1251 (2008)

nonvascular plasminogen activator effects

plasminogen activators nonvascular effects in CNS

hemostasis in the CNS

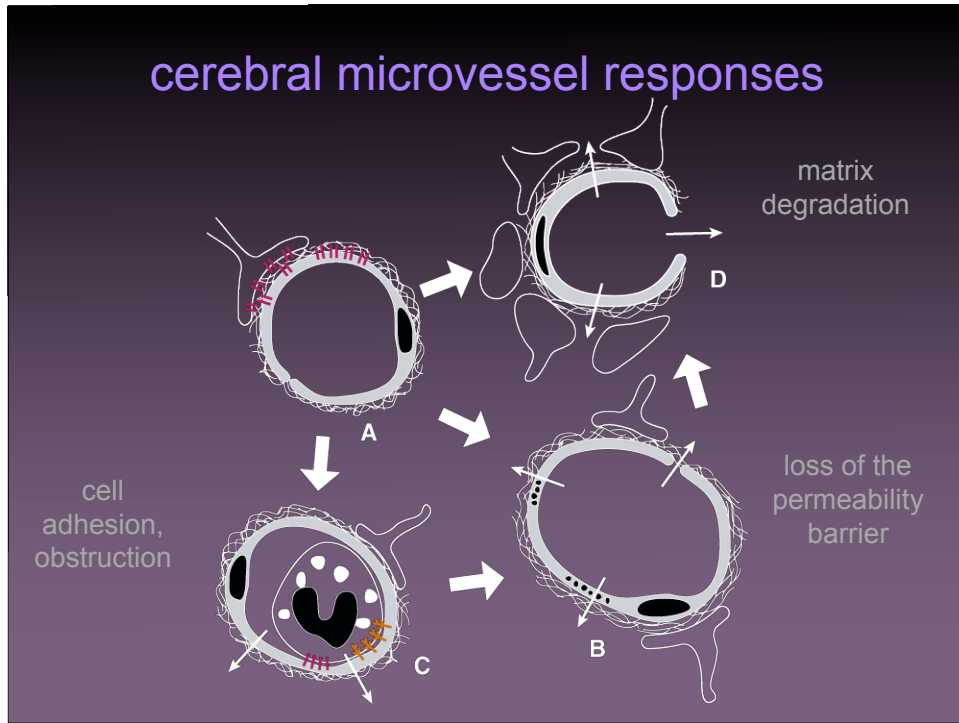
plasminogen activation and CNS
function

responses to focal ischemia

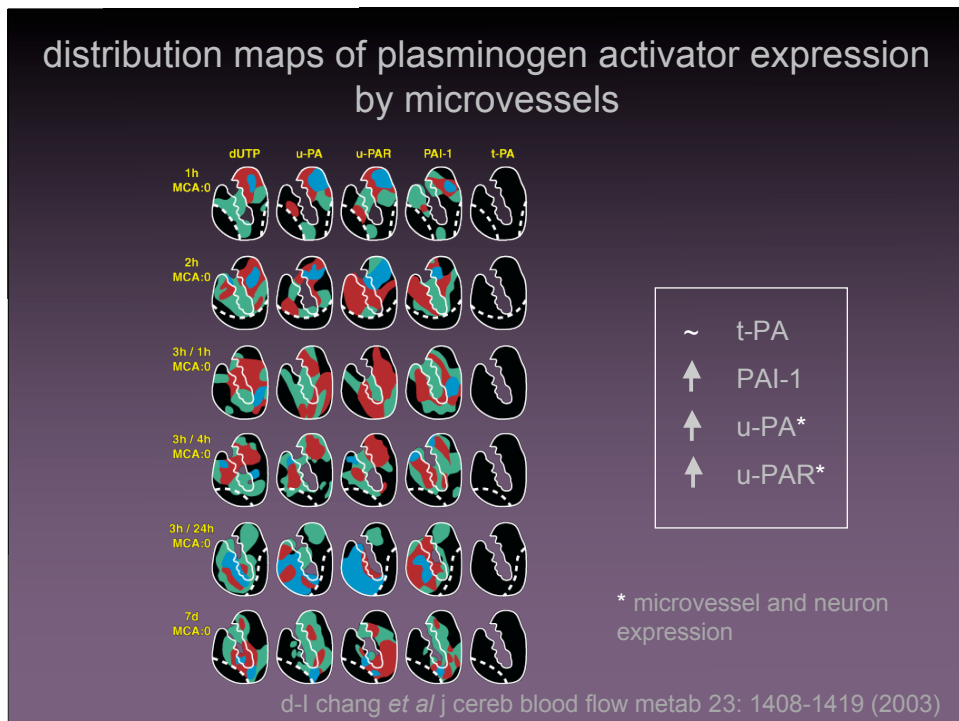
rt-PA and neuron survival

comments

cerebral microvessel responses



distribution maps of plasminogen activator expression by microvessels



plasminogen activators nonvascular effects in CNS

rt-PA stimulates excitotoxicity and shortens
neuron survival

nicole o *et al* nature med 7: 59-64 (2001)

traynelis sf, lipton sa nature med 7: 17-18 (2001)

rDS-PA vs rt-PA and neuron survival

lopez-atalya jp *et al* j cereb blood flow metab 28:
1212-1221 (2008)

dose dependency of rt-PA effects

del zoppo gj, ransom b, nedergaard m (2008-2009)

support by RO1 grants NS 26945, NS 38710, NS 53716 of the NINDS/NIH gratefully acknowledged

