ischemic stroke

north american thrombosis forum
boston, 29 september, 2007

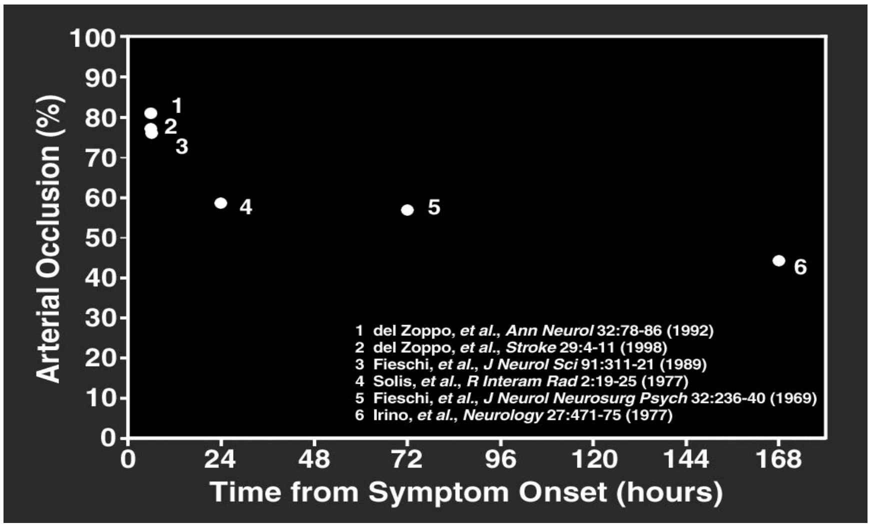
Gregory J. del Zoppo, M.D.
Department of Medicine (in Hematology)
Department of Neurology
University of Washington
Harborview Medical Center
Seattle, Washington

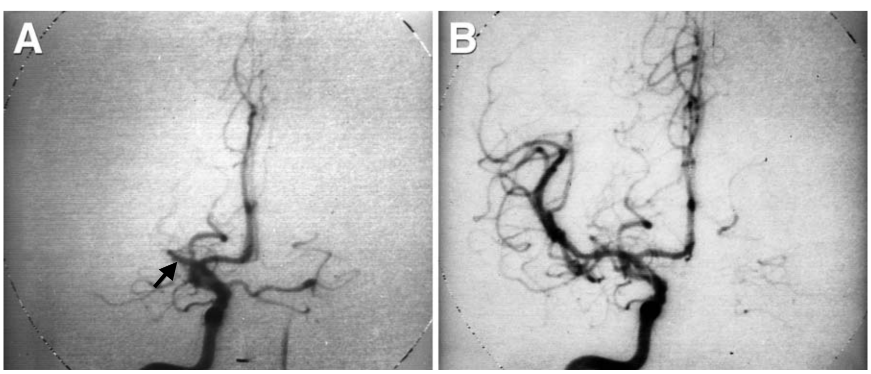
etiology of focal cerebral ischemia

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

carotid territory stroke

arterial occlusion



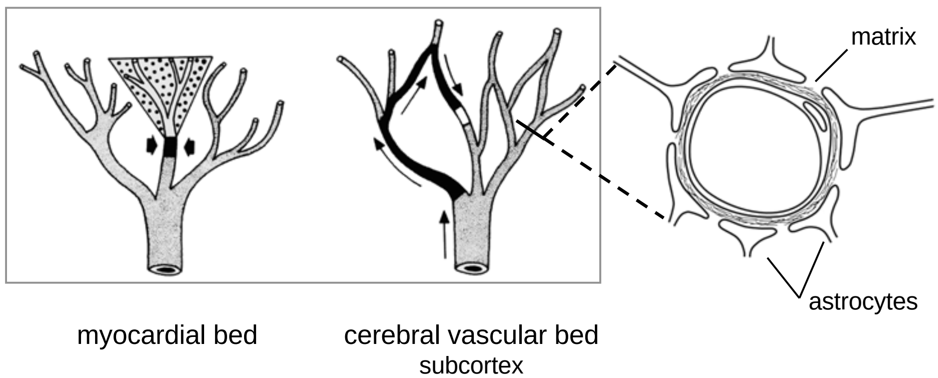


occlusion of M1 segment of MCA

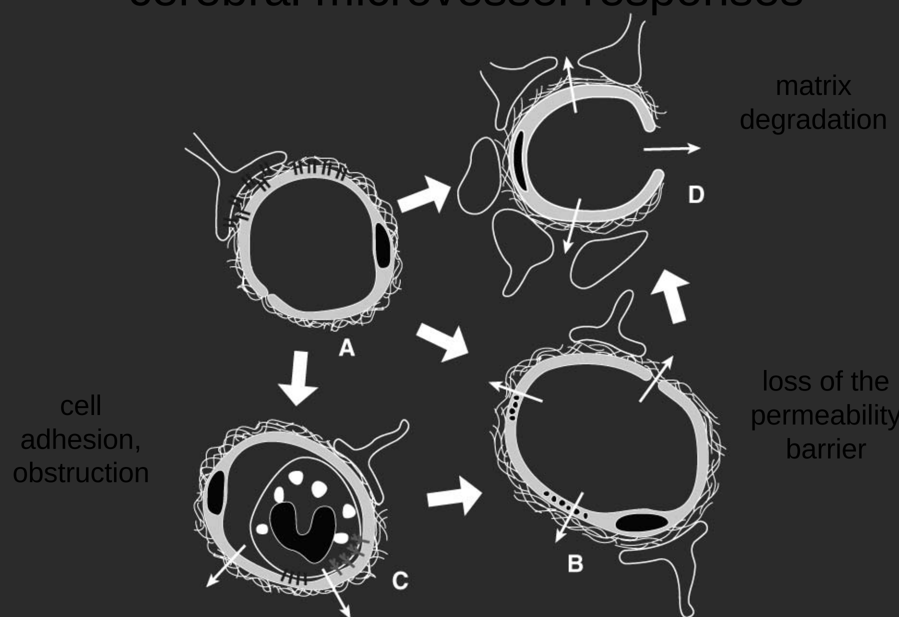
opening of occlusion with urokinase delivered locally

intrinsic collateral protection

myocardial and cerebral microvascular beds



cerebral microvessel responses



treatment approaches

1. neuroprotectant
   target: neurons
   approaches:
      Ca^{+2} channel regulation
      neurotransmitters
      cell demise pathways

2. anti-thrombotic agents
      target: vascular-dependent processes
   approaches:
      plasminogen activators
      anticoagulation
      anti-platelet agents

questions about ischemic stroke

1. are the outcomes of *in situ* thrombosis and thrombo-embolism different?
2. is the composition of a thrombotic occlusion relevant to outcome?
3. is the hemostatic system within the CNS special?
4. what are the pathophysiologic bases for the current anti-thrombotic approaches to ischemic stroke?

intracerebral hemorrhage
focal cerebral ischemia

1. hemorrhagic infarction accompanies cardioembolism
   yamaguchi t, *et al* jpn circ j 48: 50-58 (1984)
   okada y, *et al* 20: 598-603 (1989)
2. hemorrhagic risk increases with anti-thrombotic agents
3. hemorrhage can derive from collateral circulation
   ogata j *et al* stroke 20: 876-883 (1989)
4. hemorrhage is not time-dependent (in the absence of thrombolytic agents) in experimental models
   heo j-h *et al* j cereb blood flow metab 19: 624-633 (1999)

questions about hemorrhage

1. is hemorrhagic transformation a consequence of arterial recanalization?
2. does the activity of plasminogen activators (plasmin) cause hemorrhagic transformation?
3. what contribution do endogenous mechanisms of cerebral injury make?
4. do anti-platelet agents contribute beneficially or negatively to the risk of hemorrhagic transformation?

thrombotic stroke

1. acute intervention
2. secondary prevention following a signal ischemic event
   - TIA
   - completed stroke
   - PFO
3. primary prevention
   - non-valvular atrial fibrillation
   - rheumatic valvular disease
   - thrombophilic state
4. microvascular disease
   - lacunes
   - neuropsychiatric lupus

plasminogen activators in acute thrombotic stroke

study	agent	Δ(t-o) (hr)	n	recanalization %	hemorrhage %
carotid territory: intra-arterial delivery*					
del Zoppo *et al*	**SK/u-PA**	**1-24**	**20**	**90.0**	**20.0**
Mori *et al*	**u-PA**	**<7**	**22**	**45.5**	**18.2**
Matsumoto *et al*	**u-PA**	**1-24**	**40**	**60.0**	**32.5**
carotid territory: intravenous delivery**					
Yamaguchi *et al*	**rt-PA**	**<6**	**52**	**38.5**	**28.6**
von Kummer *et al*	**rt-PA**	**<6**	**22**	**59.1**	**36.4**
del Zoppo *et al*	**rt-PA**	**<8**	**93 (104)**	**34.4**	**30.8**
Mori *et al*	**rt-PA**	**<6**	**19**	**47.4**	**52.6**
	C		**12**	**16.7**	**41.7**
Yamaguchi *et al*	**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	Δ(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-2	rt-PA	409	6.0 hr	0.9 mg/kg
	C	391		

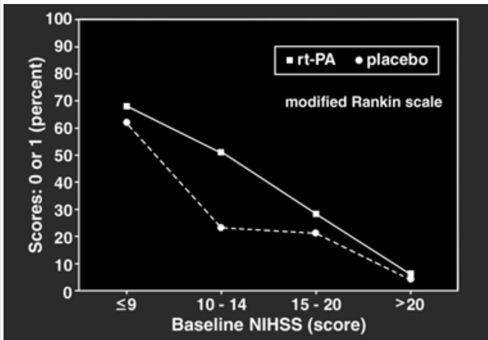
intravenous infusion

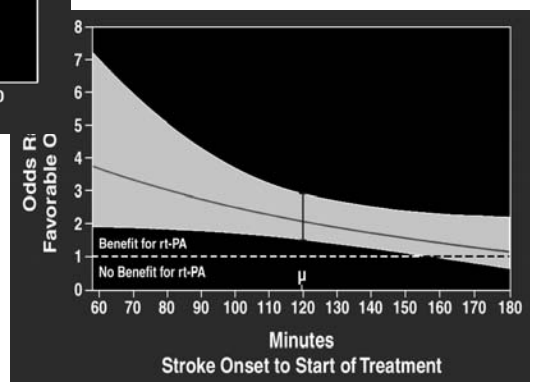
rt-PA in acute ischemic stroke
prescribed analysis

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-2	rt-PA	0 - 1	40.4%	3.8%
	C		36.6%	

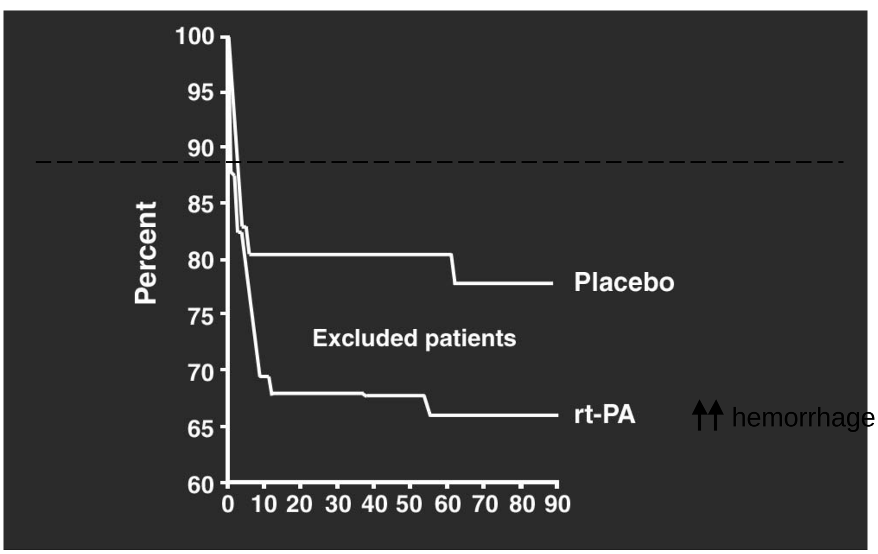
NINDS new eng j med *333*: 1581-1587 (1995)
hacke w, *et al* JAMA *274*: 1017-1025 (1995)
hacke w, *et al* lancet *352*: 1245-1251 (1998)

conditions of beneficial outcome





survival curves of “excluded” patients
ECASS



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-2	rt-PA	219	142	48	(11.7)*
	C	238	141	12	(3.1)

rscu-PA in acute ischemic stroke

study	agent	n	recanalization	hemorrhage	
				HI + PH	PH
PROACT (6 mg/kg)	rscu-PA + h	26	15 (57.7)	13 (50.0)	4 (15.4)
	C* + h	14	2 (14.3)	1 (7.1)	1 (7.1)
	heparin (100/1000)	11	9 (81.8)*	8 (72.7)*	3 (27.3)
	C	5	0 (0.0)	1 (20.0)	1 (20.0)
	heparin (2000/500)	15	6 (40.0)	3 (20.0)	1 (6.7)
	C	9	2 (22.2)	0 (0.0)	0 (0.0)
PROACT-2 (9 mg/kg)	rscu-PA + h	121	71 (65.7)		11 (10.2)
	C* + h	59	9 (18.0)		1 (1.9)

* controls: PROACT intra-arterial infusion
PROACT-2 intravenous infusion

Δ(t-o) = 6.0 hr

hemorrhage (PH) with adjuvant devices

study	device n	device	device + PA n	device + PA
rscu-PA*	--		121	11 (10.2)
control	--		59	1 (1.9)
EPAR (laser)	10	1 (10.0)	17	1 (5.9)
MERCI (retriever)	90	11 (7.7)	51	4 (7.9)

*** PROACT-2**
control: intravenous infusion heparin

after h lutsep (2005)

berlis a *et al* stroke *35*: 1112-1116 (2004)
smith ws *et al* stroke *36*: 1432-1440 (2005)

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-2	rt-PA	219	142	48	(11.7)*
	C	238	141	12	(3.1)

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
DEFUSE	rt-PA	phase III	benefit/safety (MR)
	TNK	phase III	benefit/safety
AbESTT	rt-PA +	phase II/III	benefit/safety
	rt-PA +	phase II	benefit/safety

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.

<u>no</u> <u>efficacy</u> compared to placebo

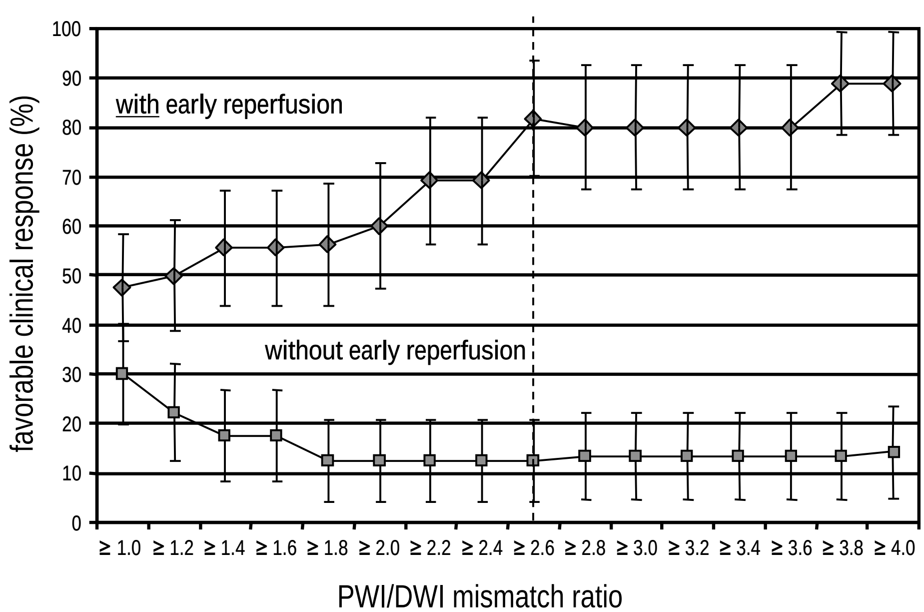
potential role of perfusion defect and territory of focal injury (diffusion)

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

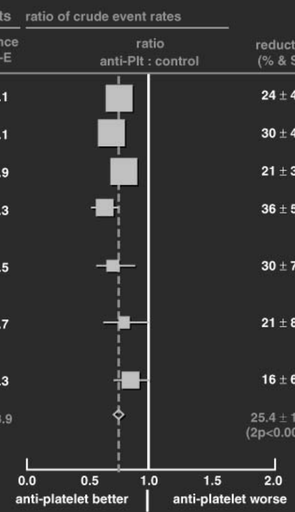
annals of neurology 60: 508-517 (2006)

optimal PWI/DWI mismatch ratio > 2.6



proportional effects of anti-platelet treatment

category of trial	no. of trials with data	events/patients: allocated anti-Plt	events/patients: adjusted controls*	anti-platelet events: obs. – exp.	anti-platelet events: variance of O-E	reduction (% & SD)
Prior MI	12	1343/9984 (13.5%)	1706/10022 (17.0%)	-158.9	567.1	24 ± 4%
Acute MI	10	988/9450 (10.5%)	1348/9434 (14.3%)	-180.9	510.1	30 ± 4%
Prior stroke	22	2126/11896 (17.9%)	2539/11877 (17.9%)	-152.9	654.9	21 ± 3%
Other cardiac disease: non-embolic	46	528/7734 (6.8%)	747/7691 (9.7%)	-110.5	247.3	36 ± 5%
Other cardiac disease: embolic	12	276/2447 (11.3%)	365/2481 (14.7%)	-45.4	128.5	30 ± 7%
Peripheral arterial disease	39	273/4361 (6.3%)	329/4382 (7.5%)	-28.0	115.7	21 ± 8%
Other high risk	38	470/4966 (9.5%)	534/4907 (10.9%)	-34.7	205.3	16 ± 6%
Total	179	6004/50838 (11.8%)	7569/50774 (14.9%)	-711.3	2428.9	25.4 ± 1.8% (2p<0.00001)



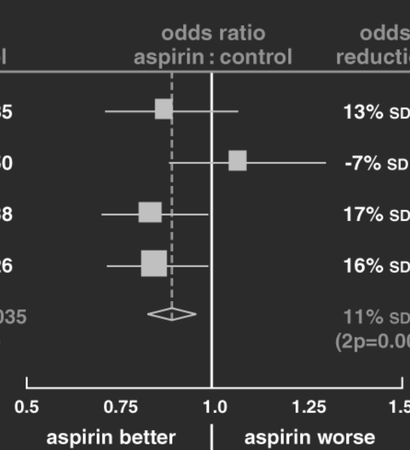
99% or 95% confidence intervals

heterogeneity between 7 categories: $\chi^2_6 = 14.1$; p = 0.08

*vascular events in "high risk" trials

effect of aspirin in ischemic stroke: time from symptom onset

Δ(t-o)	events/patients: aspirin	events/patients: control	odds reduction
0-6	323/2844	358/2785	13% SD 8
7-12	379/3455	367/3550	-7% SD 8
13-24	435/5641	505/5538	17% SD 6
25-48	498/8092	589/8126	16% SD 6
Total	1641/20,055 (8.2%)	1823/20,035 (9.1%)	11% SD 3 (2p=0.001)



99% or 95% limits

heterogeneity test: $\chi^2_3 = 7.5$; p = 0.06

antiplatelet agents: TIAs and ischemic stroke

study	agent(s)
AICLA	ASA or ASA/dipyridamole*
UK-TIA	ASA x 2*
SALT	ASA*
TASS	ticlopidine* vs. ASA
CATS	ticlopidine*
CAPRIE	clopidogrel vs. ASA
ESPS 2	ASA/dipyridamole* vs. ASA

anti-platelet agents in TIA and ischemic stroke

study	agent	n	stroke	mortality
ACCSG (1985)	ASA / dipyr	448	53 (11.8)	46 (10.3)
	ASA	442	60 (13.6)	38 (8.6)
ESPS (1987)	ASA / dipyr	1 250	114 (9.1)*	108 (8.6)*
	placebo	1 250	184 (14.7)	156 (12.5)
ESPS-2 (1996)	ASA / dipyr	1 649	157 (9.5)*	202 (12.3)
	ASA	1 649	206 (12.5)	182 (11.0)
	dipyr	1 654	211 (12.8)	188 (11.4)
	placebo	1 650	250 (15.2)	185 (11.2)

clopidogrel-ASA comparison studies

CLASSICS	coronary artery stent	ASA
WATCH	chronic heart failure	warfarin
CURE	coronary artery event	ASA
MATCH	ischemic stroke +	clopidogrel
ESPRIT	ischemic stroke +	ASA ± dipyr
PRoFESS	ischemic stroke	ASA / dipyr (± ARB)

Prevention Regimen for Effectively Avoiding Second Strokes

phase III safety/efficacy trial of competing antiplatelet agents ± angiotensin receptor inhibitor to prevent recurrent stroke

patients > 55 years with ischemic stroke within 90 days of study entry

primary outcome:
time to first recurrent stroke

secondary outcome (composite):
time to first non-fatal stroke, non-fatal MI, or vascular death

projected population: 15,500 patients

non-valvular atrial fibrillation

studies

AFASAK

SPAF

BAATAF

CAFA

SPAFII

SPINAF

EAFT

SPAFIII

non-valvular atrial fibrillation

study	agent	patients	stroke	mortality
AFASAK	warfarin	335	5(0)	~~
	ASA	336	17(3)	~~
	placebo	336	19(2)	~~
SPAF	warfarin/ASA	393	7(0)	14
	placebo	195	17(1)	8
	ASA	517	18(1)	31
	placebo	528	34(4)	39
BAATAF	warfarin	212	2(0)	11
	placebo	208	(0)	26
CAFA	warfarin	187	4(1)	7
	placebo	191	9(2)	6
SPAFII	warfarin	358	13(1)	36
	ASA	357	19(2)	41
	warfarin	197	13(1)	26
	ASA	188	18(0)	24
SPAFIII	warfarin INR 2.0-3.0	523	11(0)	35
	warfarin INR 1.2-1.5	521	43(1)	42

SPORTIF III

hypothesis: ximelagatran is not inferior to well-controlled warfarin for prophylaxis against systemic embolism in nonvalvular AF

design: prospective randomized blinded, two-arm (3410 patients)

warfarin, INR 2.0-3.0 ximelagatran 36 mg, twice daily

primary outcome: stroke or systemic embolism

results:

	primary event rate (ITT)	minor + major hemorrhages
warfarin	2.3%/year	29.8%/year
ximelagatran	1.6%/year	25.8%/year

conclusion: ximelagatran not inferior to warfarin in this setting

atrial fibrillation

warfarin *vs* clopidogrel

phase III prospective trial terminated due to safety concerns

incidence of stroke increased 75% in clopidogrel arm over warfarin arm

report by Sanofi, late 2005

anticoagulants in early stroke

study	agent	n	Δ(t-o)	follow-up
FISS (1995)	nadroparin (h)	100	48 hr	6 mo
	nadroparin (l)	101		
	C	105		
FISS-bis (1998)	nadroparin (h)	245	24 hr	6 mo
	nadroparin (l)	272		
	C	250		
IST* (1997)	heparin	9 716	48 hr	14 d
	no heparin	9 717		
TOAST (1998)	danaparoid	641	24 hr	3 mo
	C	634		

* multifactorial design aspirin / heparin / placebo

anticoagulants in early stroke

study	agent	n	Δ(t-o)	follow-up
HAEST (2000)	dalteparin	224	24 hr	3 mo
	ASA	225		
TOPAS (2001)	certoparin (16)	97	24 hr	3 mo
	certoparin (10)	103		
	certoparin (06)	102		
	certoparin (03)	98		

* x 1,000 anti-FXa/day

warfarin-aspirin in recurrent stroke study (WARSS)

outcome	events		*p*
	warfarin	ASA	
total	1103	1103	
recurrent stroke/demise	196	176	0.250
with major hemorrhage	222	196	0.160
hemorrhage			
major	38	30	0.390
minor	261	188	< 0.001

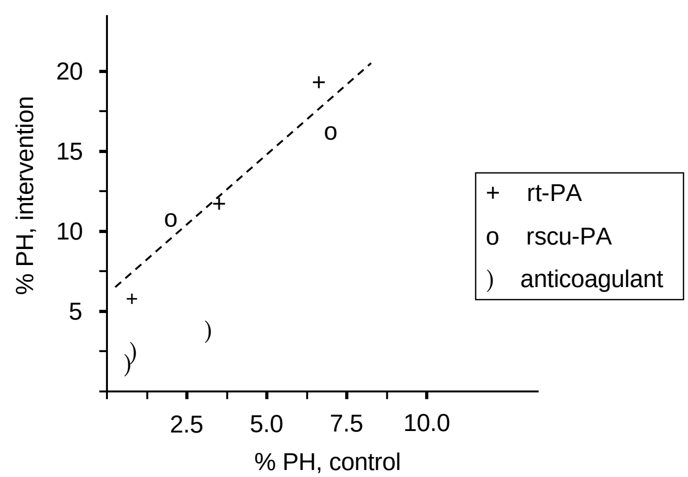
thrombotic stroke

1. acute intervention
2. secondary prevention following a signal ischemic event
   - TIA
   - completed stroke
   - PFO
3. primary prevention
   - non-valvular atrial fibrillation
   - rheumatic valvular disease
   - thrombophilic state
4. microvascular disease
   - lacunes
   - neuropsychiatric lupus

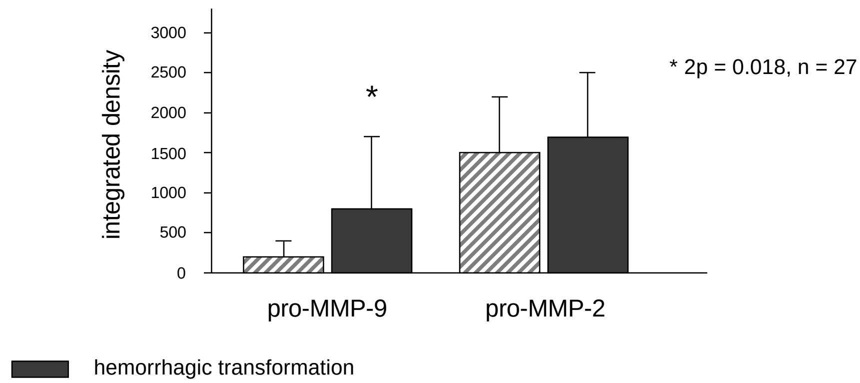
hemorrhagic transformation

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



pro-MMP-9 and hemorrhagic transformation



heo j-h *et al* j cereb blood flow metab 19: 624-633 (1999)

pro-MMP-9 and hemorrhagic transformation

1. hemorrhage accompanying ischemia in primates is associated with an increase in tissue pro-MMP-9

   heo j-h *et al* j cerebr blood flow metab 19: 624-633 (1999)

2. rt-PA-related hemorrhage associated with increased pro-MMP-9 in rats

   sumii t, lo eh *et al* stroke 33: 831-836 (2002)

3. plasma pro-MMP-9 is increased following spontaneous ICH in patients

   abilleira s *et al* j neurosurgery 99: 65-70 (2003)

4. increased pro-MMP-9 is associated with CAA^{+} vessel microhemorrhage in aged APPsw transgenic mice

   lee jm *et al* ann neurol 54: 379-382 (2003)

ischemic stroke general observations

1. microvascular responses to focal ischemia and the inciting events involve alterations in hemostasis
2. treatment approaches are stroke sub-type dependent
3. acute primary interventions currently include systemic infusion rt-PA within 3 hours of symptom onset according to strict criteria
4. secondary prevention and primary treatment involve anti-platelet agents and anticoagulants, respectively
5. understanding of the pathophysiologic bases for evolving ischemic injury is still limited

supported by RO1 grants NS 26945, NS 38710, and NS 53716 of the NINDS/NIH