Stroke Update: New Tricks for an Old Dogma

Patrick D. Lyden, MD, FAAN, FANA, FAHA

Professor, Neurology

Louis and Carmen Warschaw Chair in Neurological Research

Presenter Disclosure Information

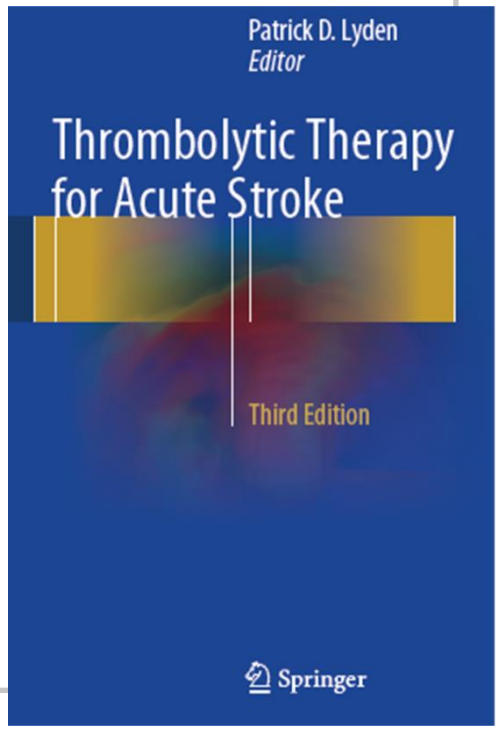
Patrick D. Lyden

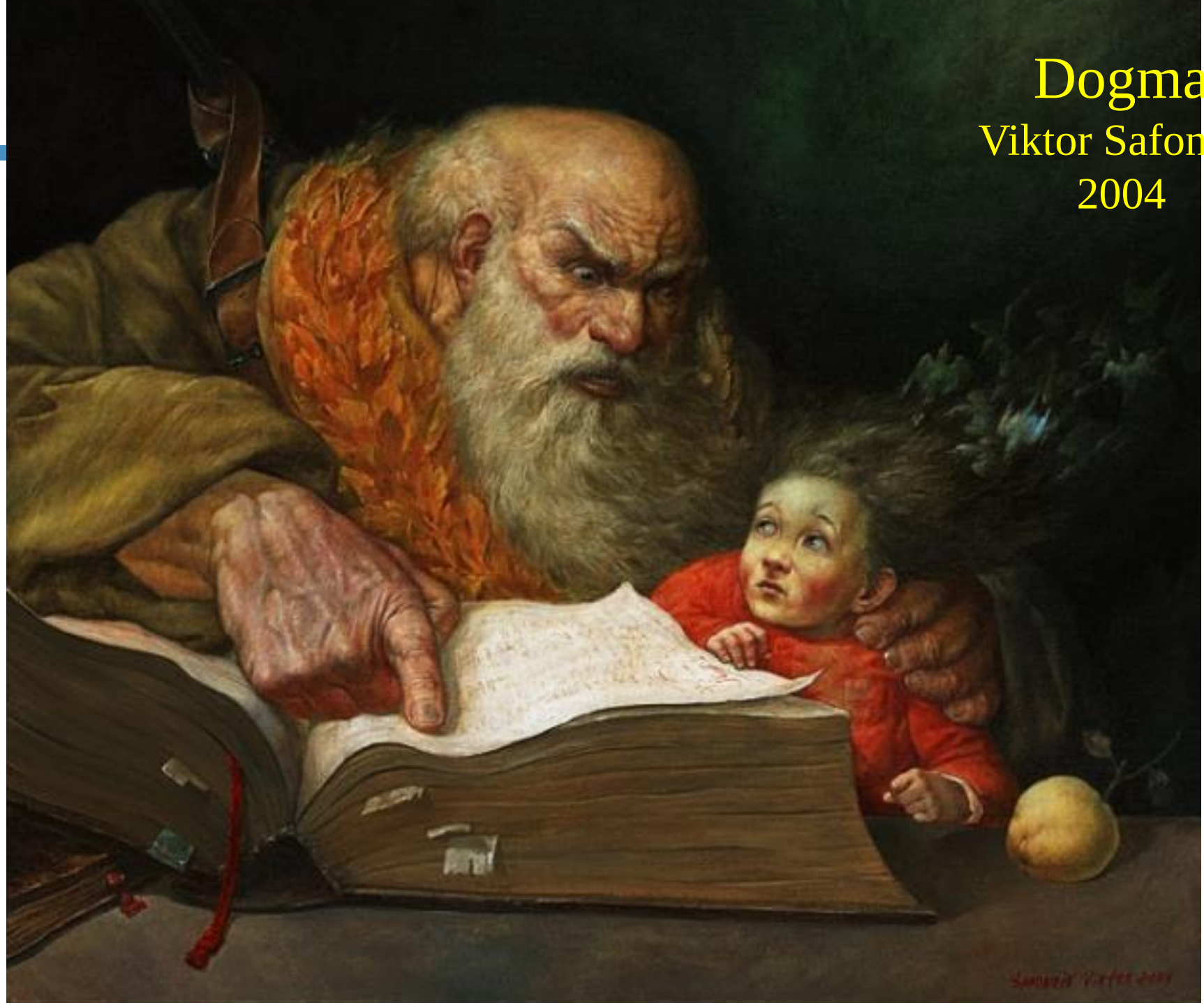
New Tricks for an Old Dogma

NINDS	**R01 NS075930 (PI)**
NINDS	**U01 NS088312 (PI)**
NINDS	**U24 NS113452 (PI)**

FINANCIAL DISCLOSURE:
I have no relationship with any company associated with thrombolysis or thrombectomy

UNLABELED/UNAPPROVED USES DISCLOSURE:
I will describe uses of a number of drugs based on dogma and very little science.



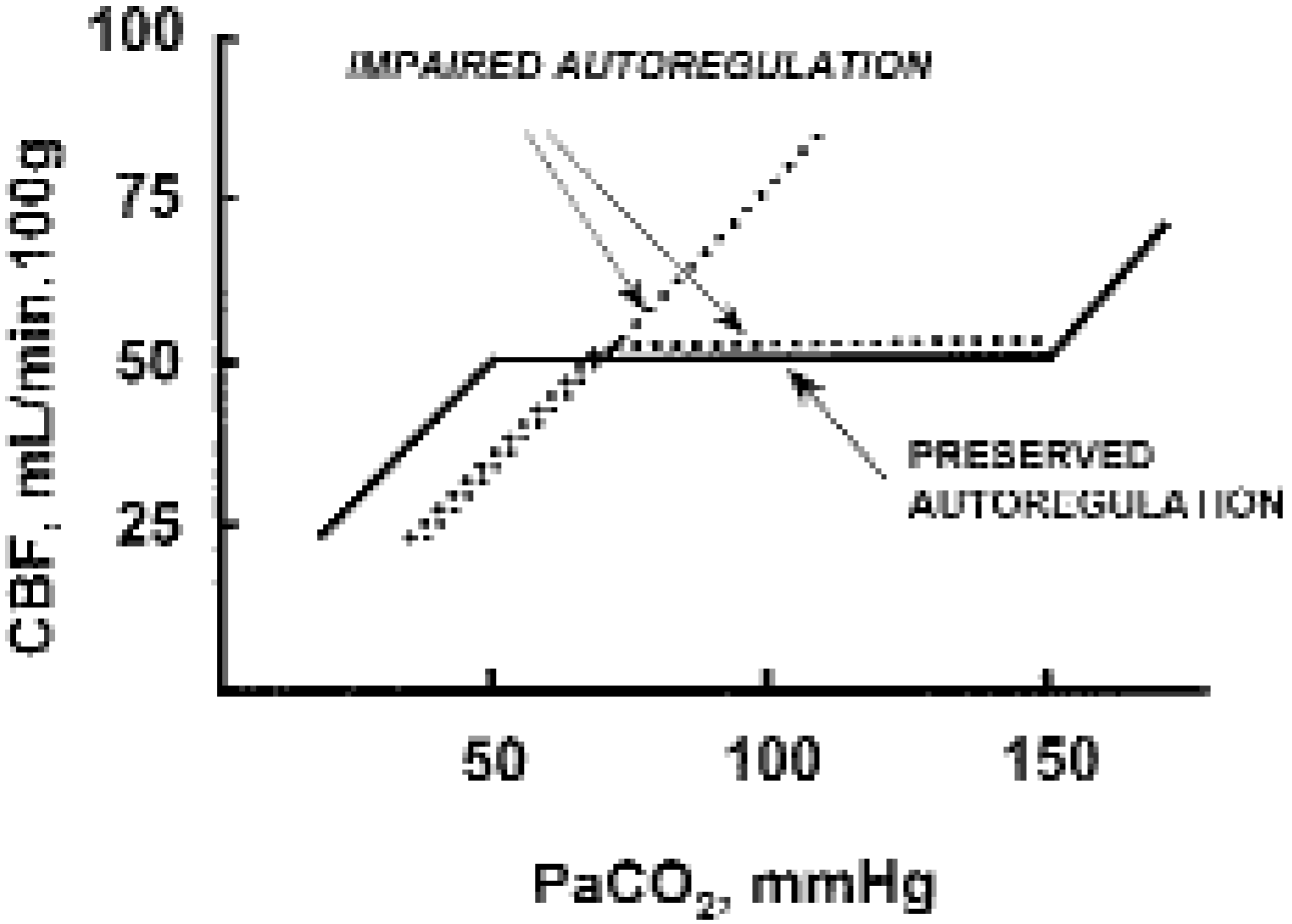


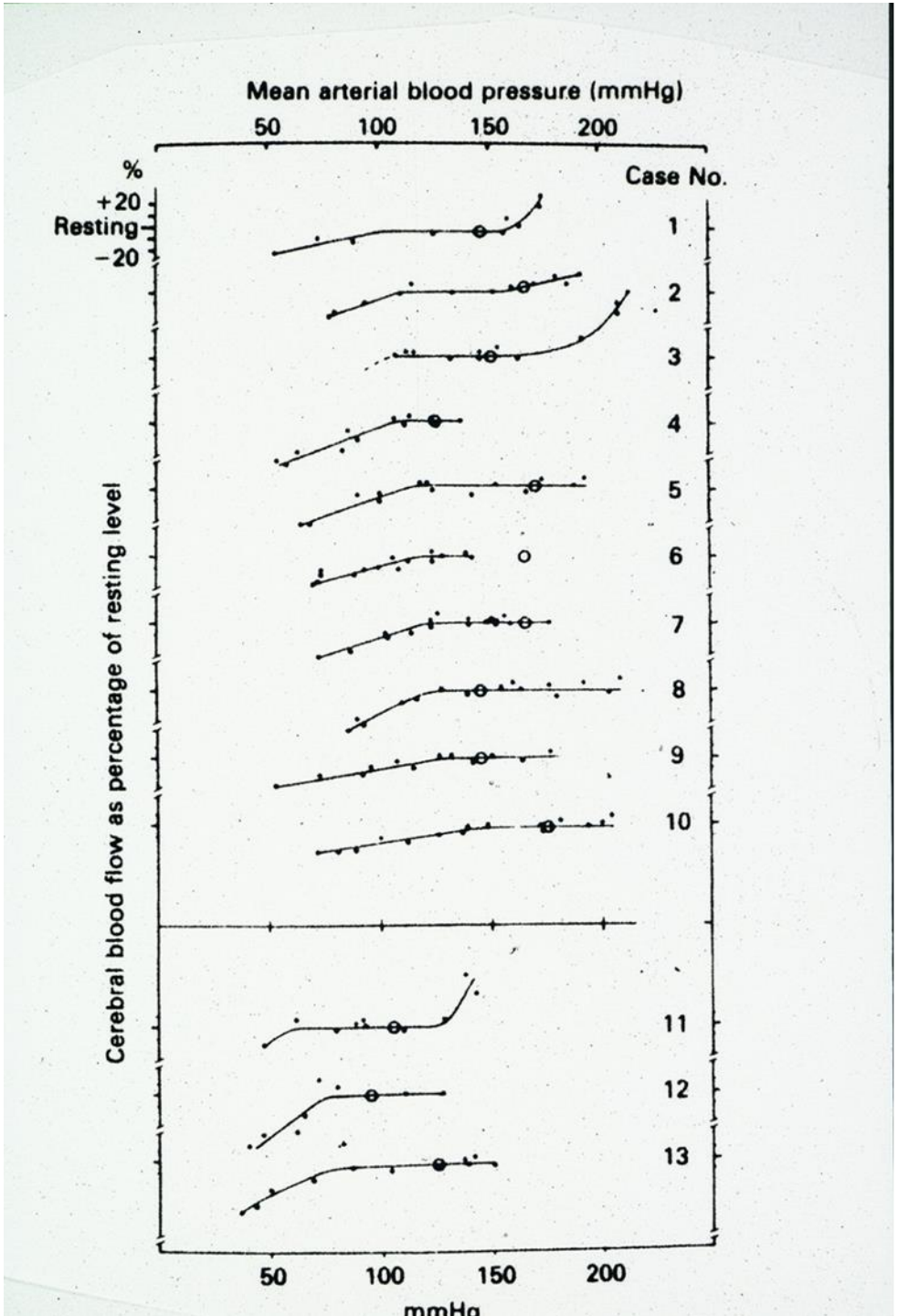
Dogma

Viktor Safonkin

2004

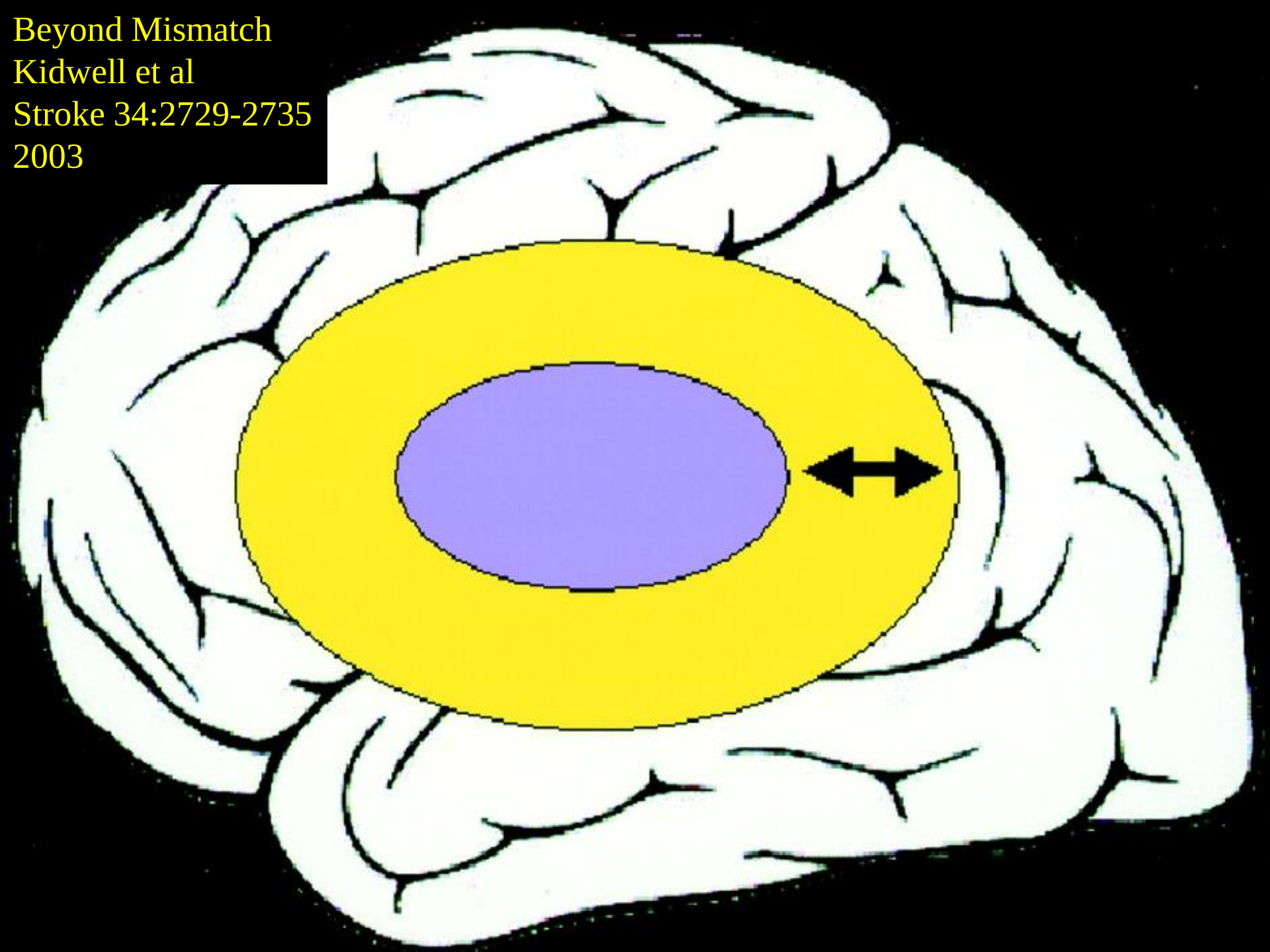
CBF in pathological states



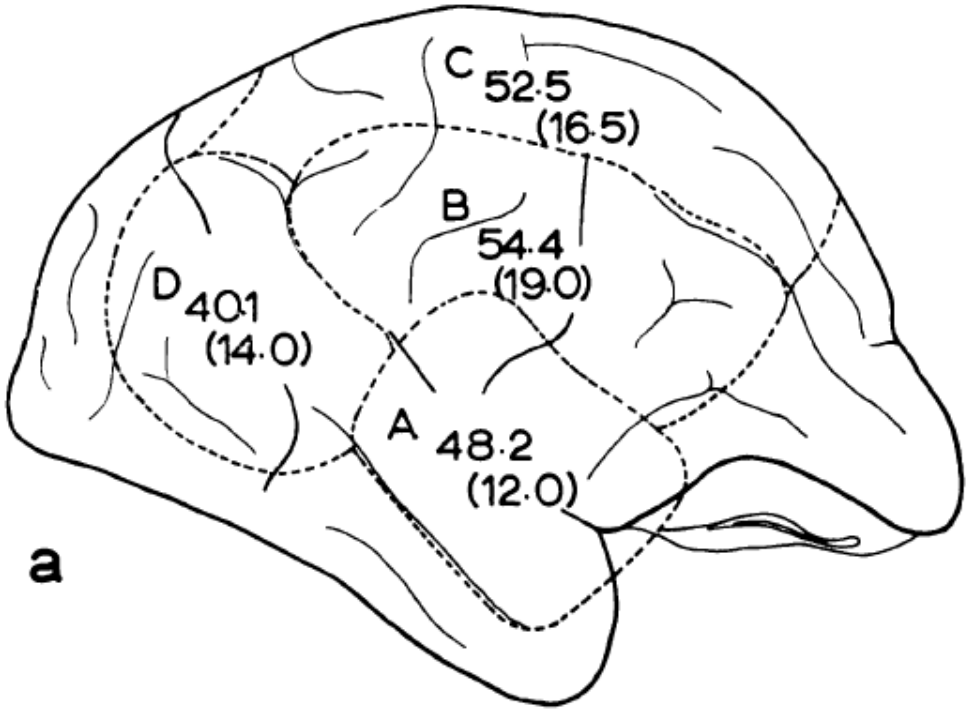


Strandgaard et al
Autoregulation of Brain Circulation in Severe Arterial Hypertension
Br Med J 1973
1(5852):507-510

Beyond Mismatch
Kidwell et al
Stroke 34:2729-2735
2003

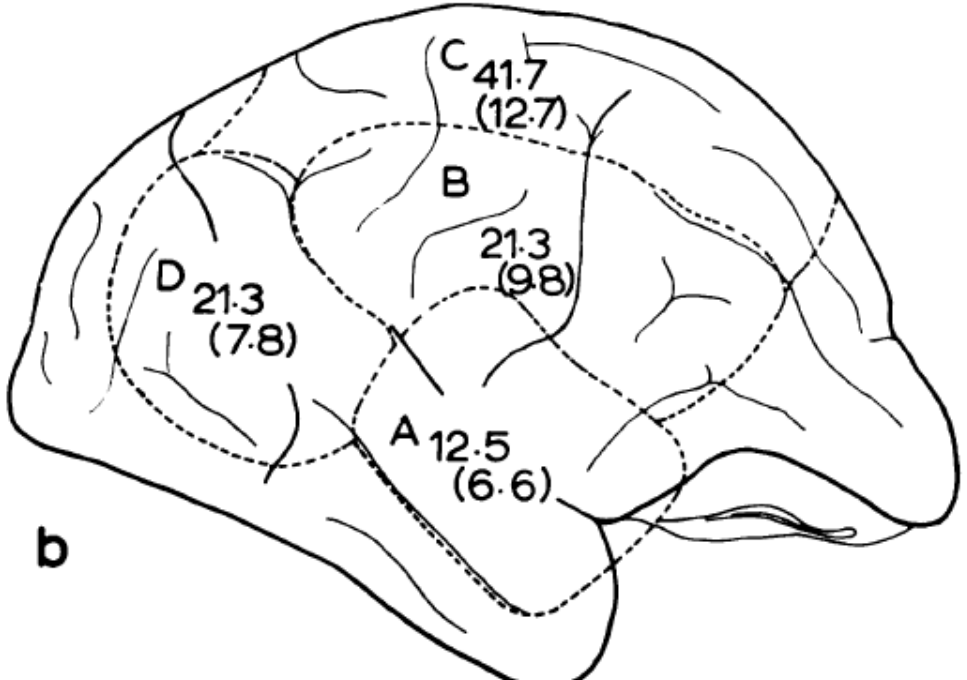


J Clin Pathol Suppl (R Coll Pathol). 1977; 11: 149–154.

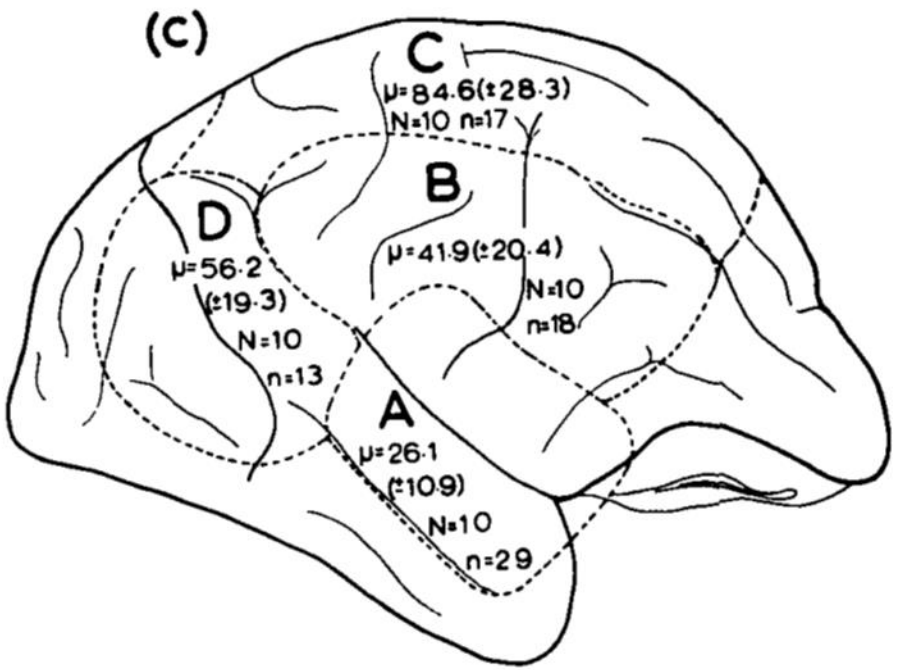


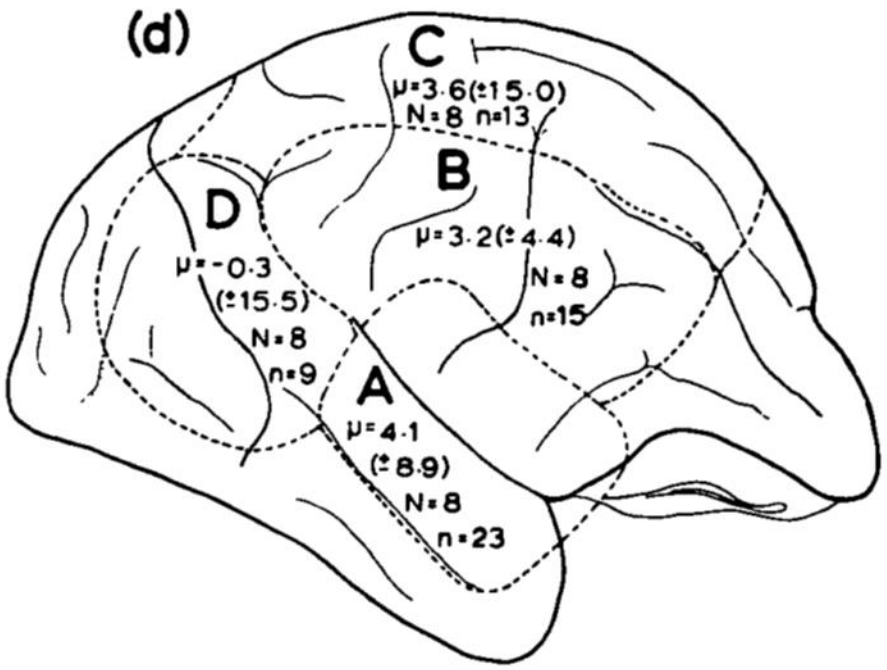
Baseline

Where's the data?

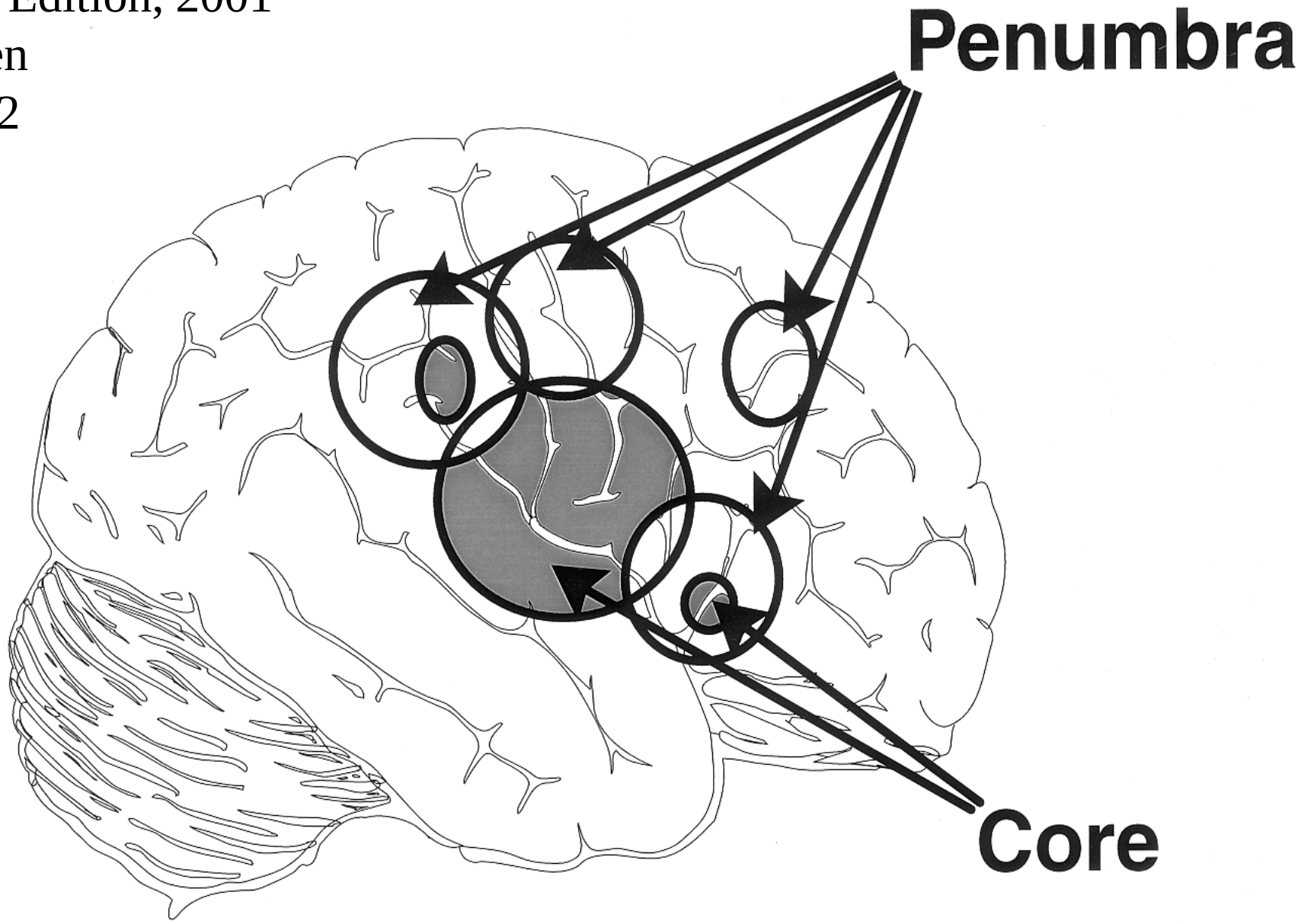


After Occlusion

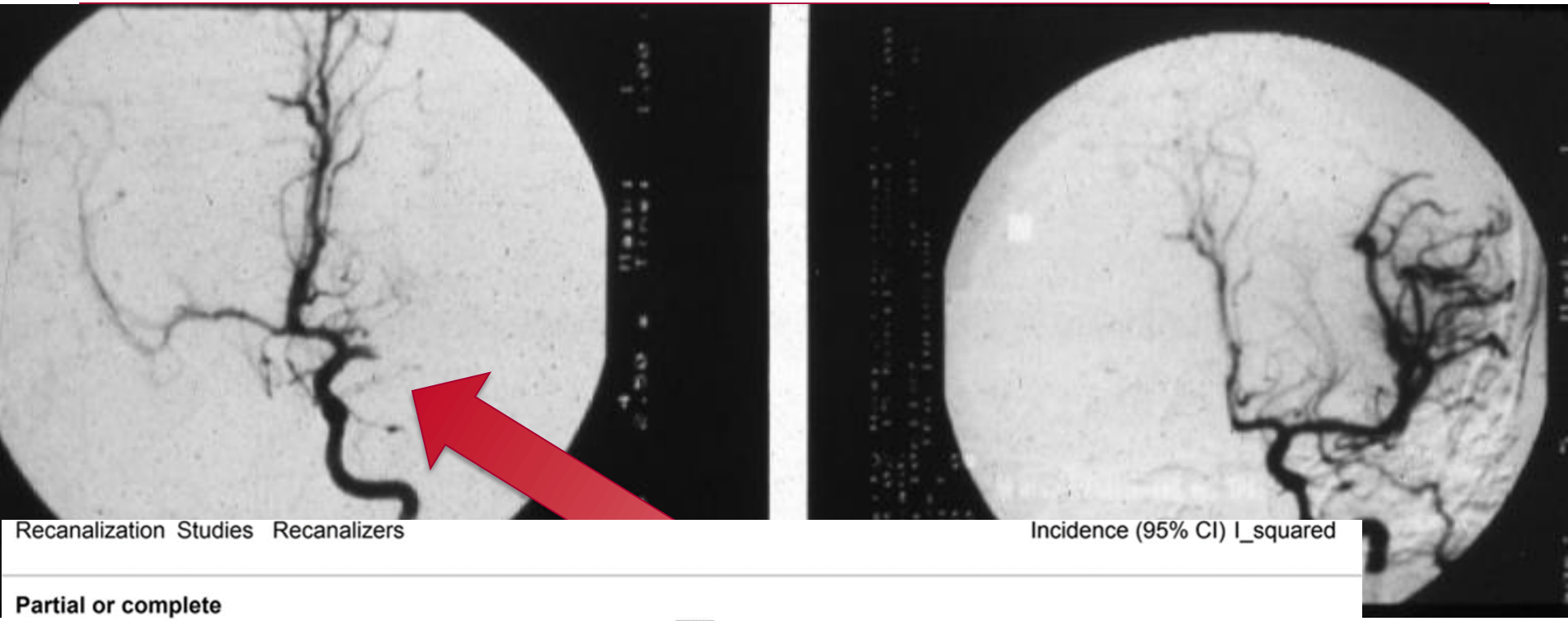

(c)
C
μ=84.6(±28.3)
N=10 n=17
B
μ=41.9(±20.4)
N=10
n=18
D
μ=56.2
(±19.3)
N=10
n=13
A
μ=26.1
(±10.9)
N=10
n=29


(d)
C
μ=3.6(±15.0)
N=8 n=13
B
μ=3.2(±4.4)
N=8
n=15
D
μ=-0.3
(±15.5)
N=8
n=9
A
μ=4.1
(±8.9)
N=8
n=23

Thrombolytic Therapy for Acute Stroke
First Edition, 2001
Lyden
Fig. 2

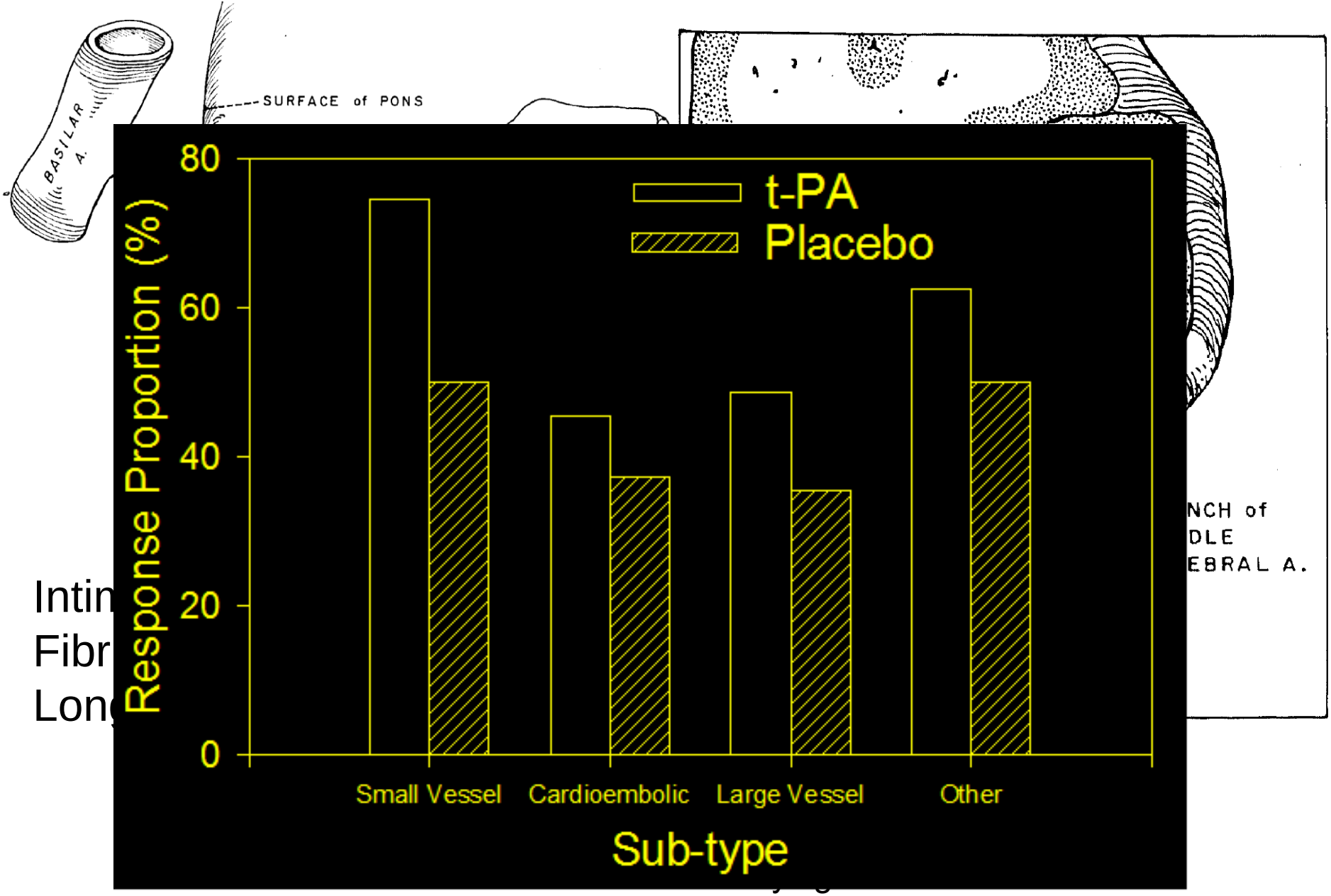


That occlusion will never open



Recanalization	Studies	Recanalizers	Incidence (95% CI)	I_squared
Partial or complete				
Any occlusion	23	667/1927	33% (27, 40)	89%
M1	21	342/942	35% (28, 42)	80%
M2-M3	16	189/369	52% (39, 64)	77%
ICA	16	53/328	13% (6, 22)	67%
Basilar artery	5	8/49	13% (0, 35)	49%

Stroke. 2016;47:2409–2412

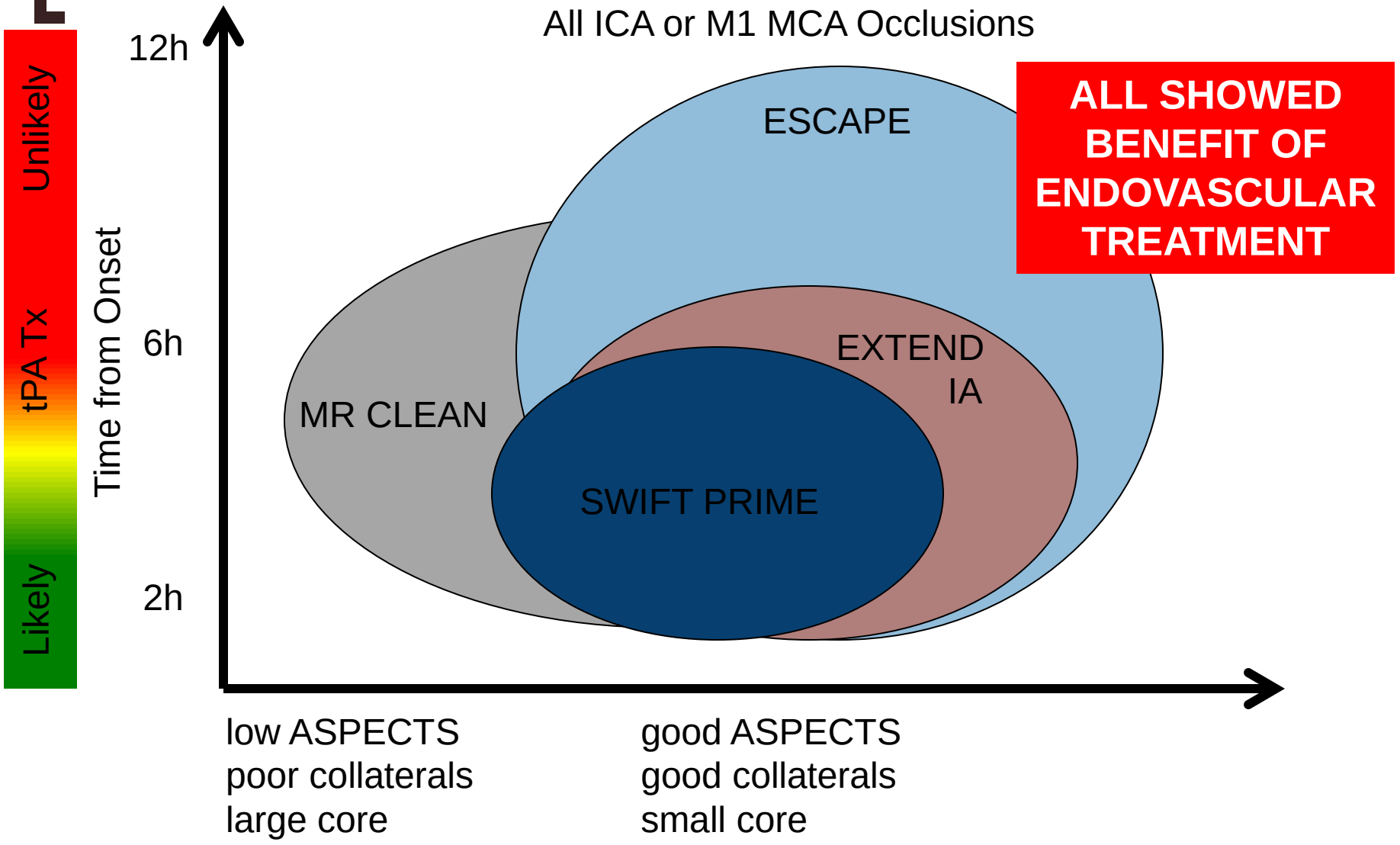


Intim
Fibr
Long

Acta neuropath. (Berlin) 12, 1-15, 1969

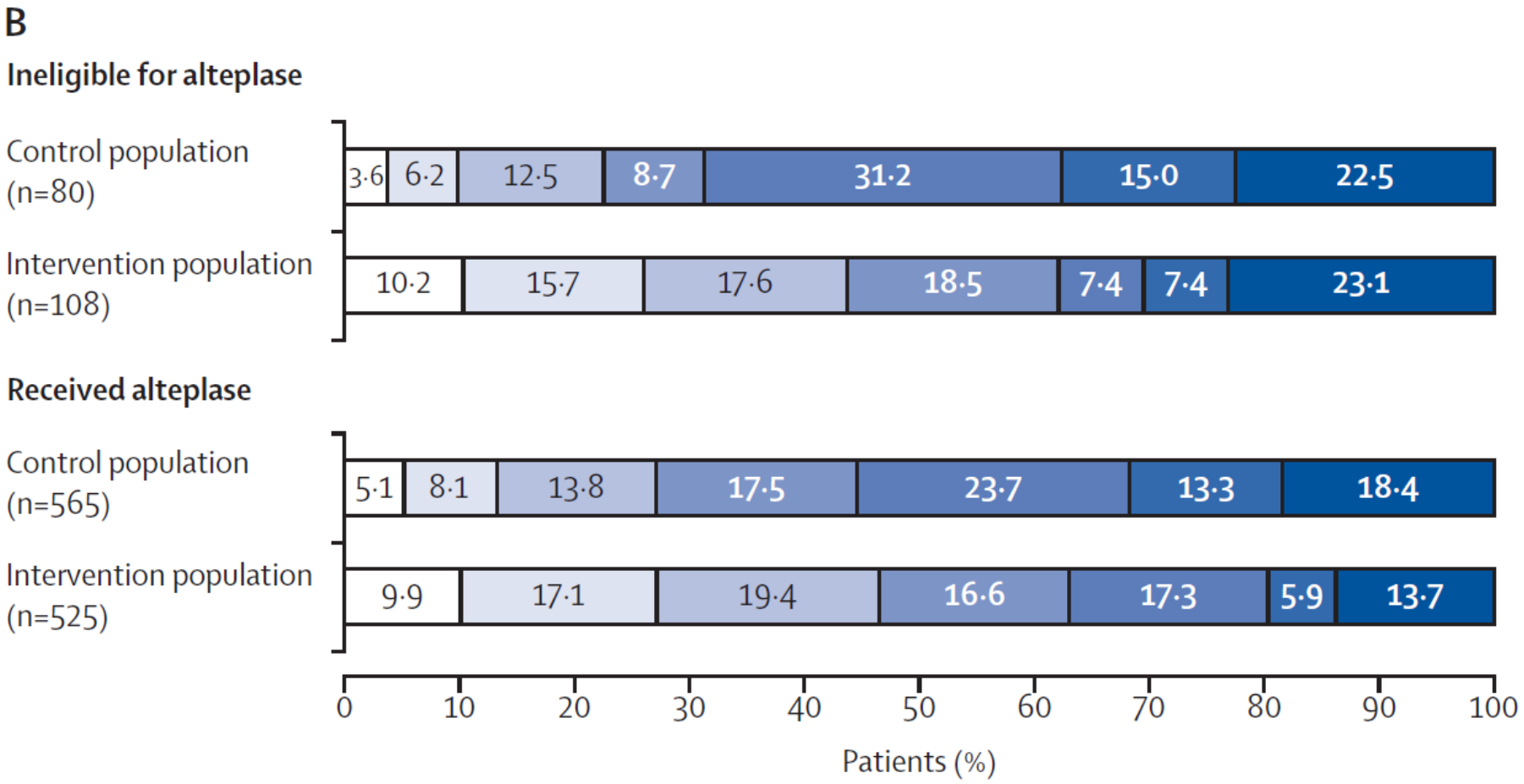
Thrombectomy

IA STUDY POPULATION



Slide credit: M. Goyal ESCAPE Trial Presentation

Meta-analysis
HERMES Collaboration, Goyal et al. Lancet 2016;387:1723-31



Meta-analysis
HERMES Collaboration, Goyal et al. Lancet 2016;387:1723-31

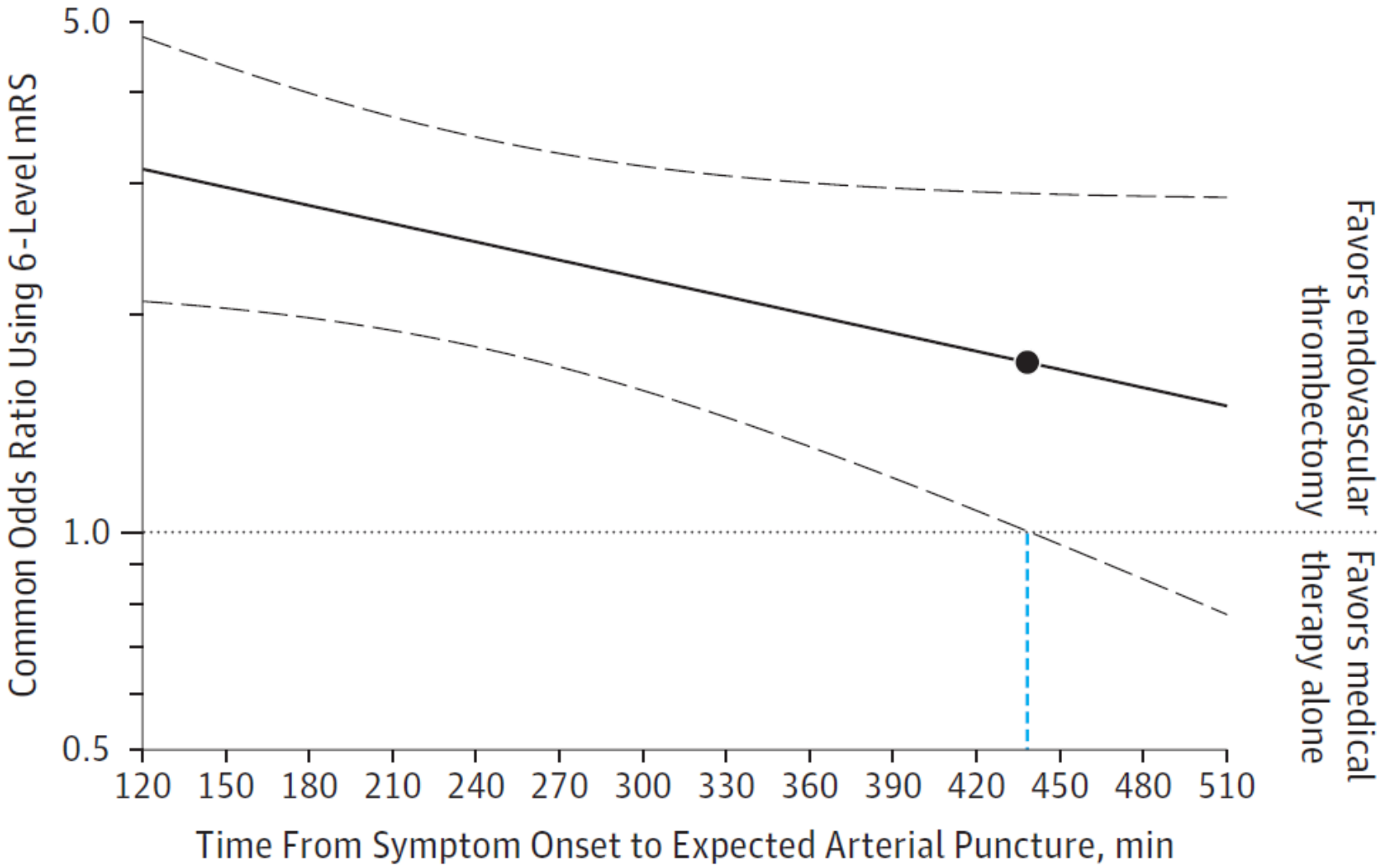
	Intervention population	Control population	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
Symptomatic intracranial haemorrhage	4·4% (28/634)	4·3% (28/653)	1·07 (0·62–1·80); p=0·81	1·07 (0·62–1·84); p=0·81
Parenchymal haematoma type 2	5·1% (32/629)	5·3% (34/641)	1·04 (0·64–1·69); p=0·88	1·04 (0·63–1·72); p=0·88
Mortality	15·3% (97/633)	18·9% (122/646)	0·82 (0·62–1·08); p=0·15	0·73 (0·47–1·13); p=0·16

Data show the proportion of patients with outcome (n/N), unless oth

***Table 4*: Safety outcomes at 90 days**

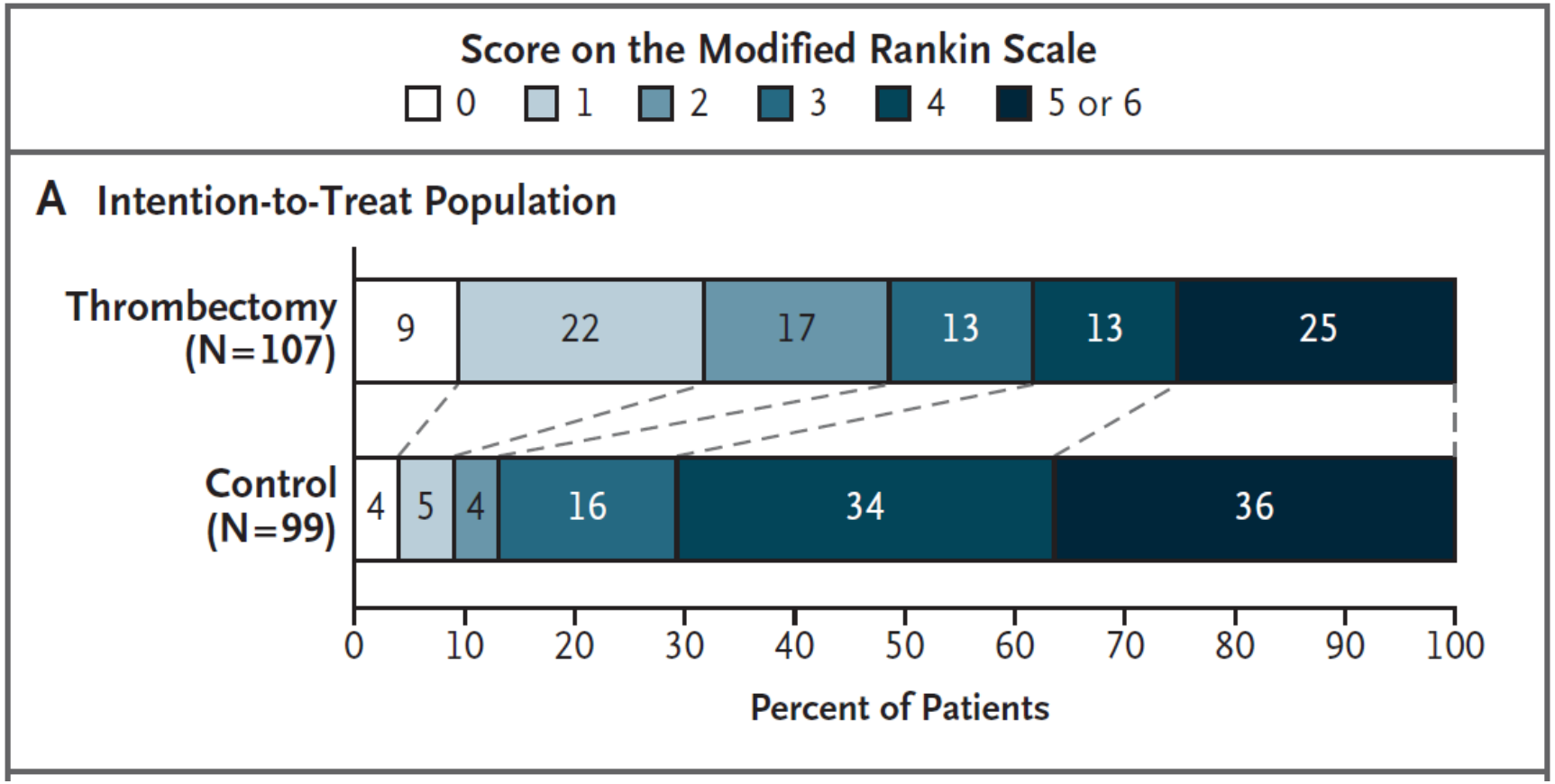
HERMES

Saver et al. JAMA. 2016;316:1279-1288



DAWN

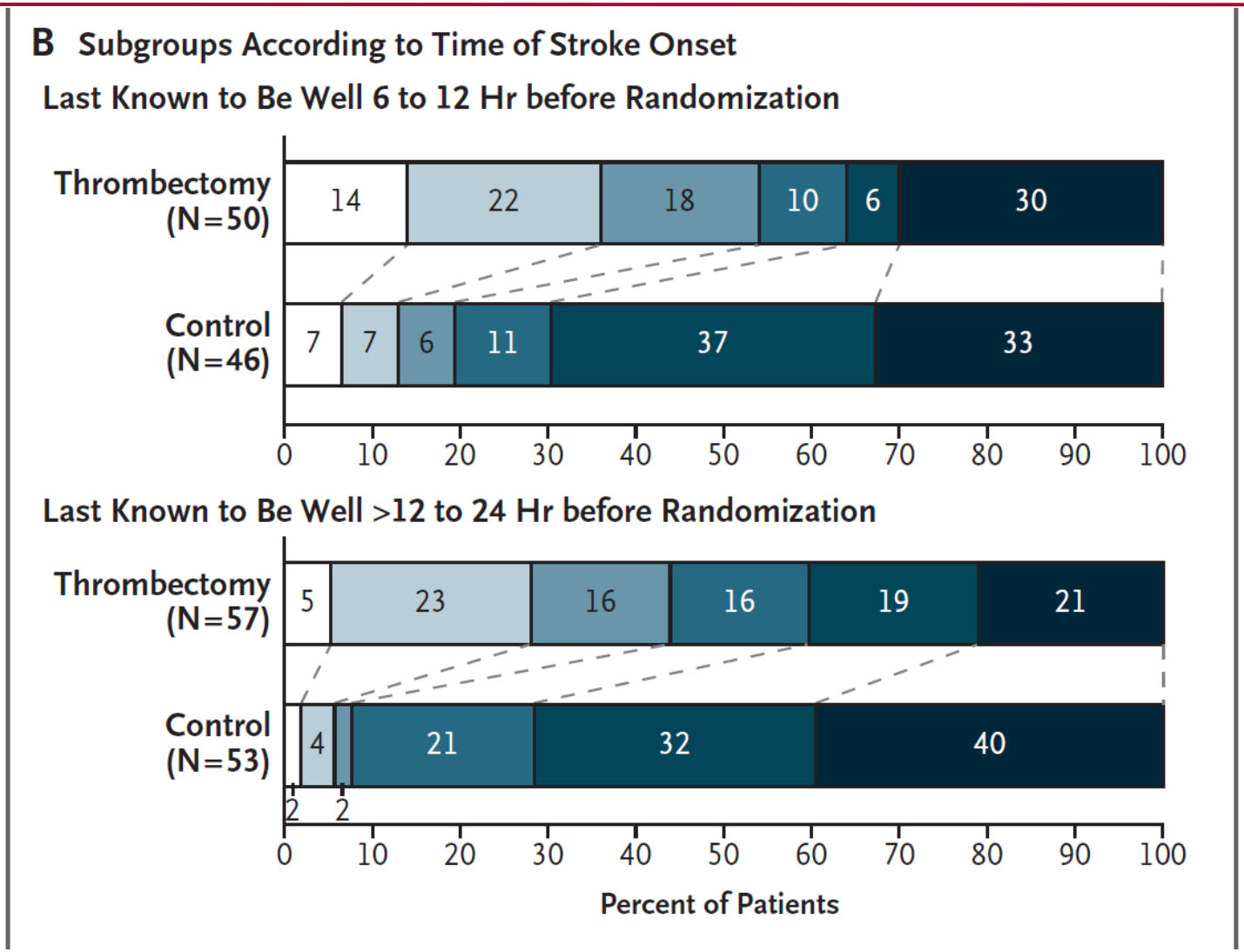
Nogueira et al. NEJM 2017 **DOI: 10.1056/NEJMoa1706442**



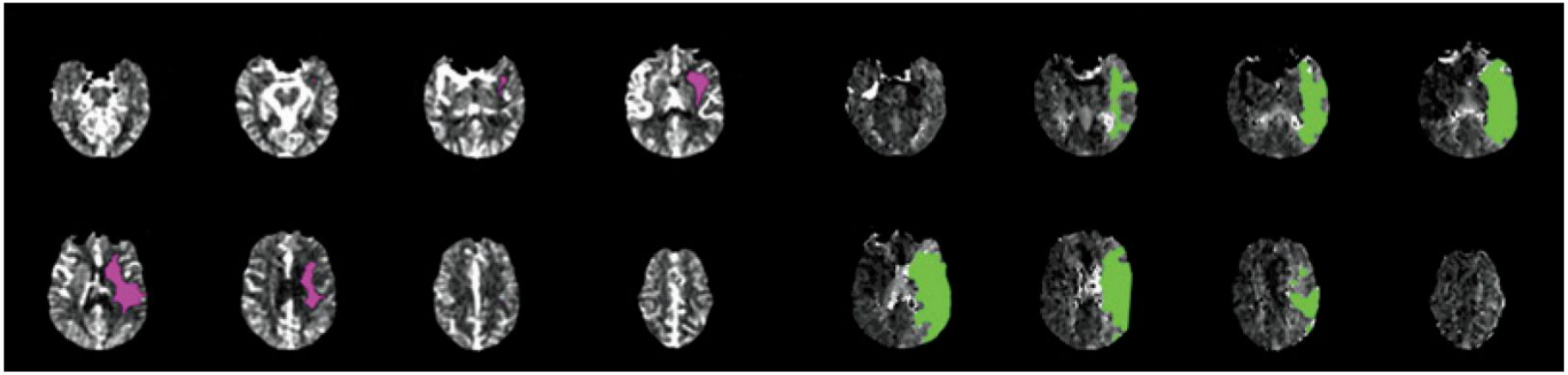
6-24 hours LKNW

DAWN

Nogueira et al. NEJM 2017 **DOI: 10.1056/NEJMoa1706442**



DEFFUSE-3
Albers et al. NEJM 2018; 378:708-18

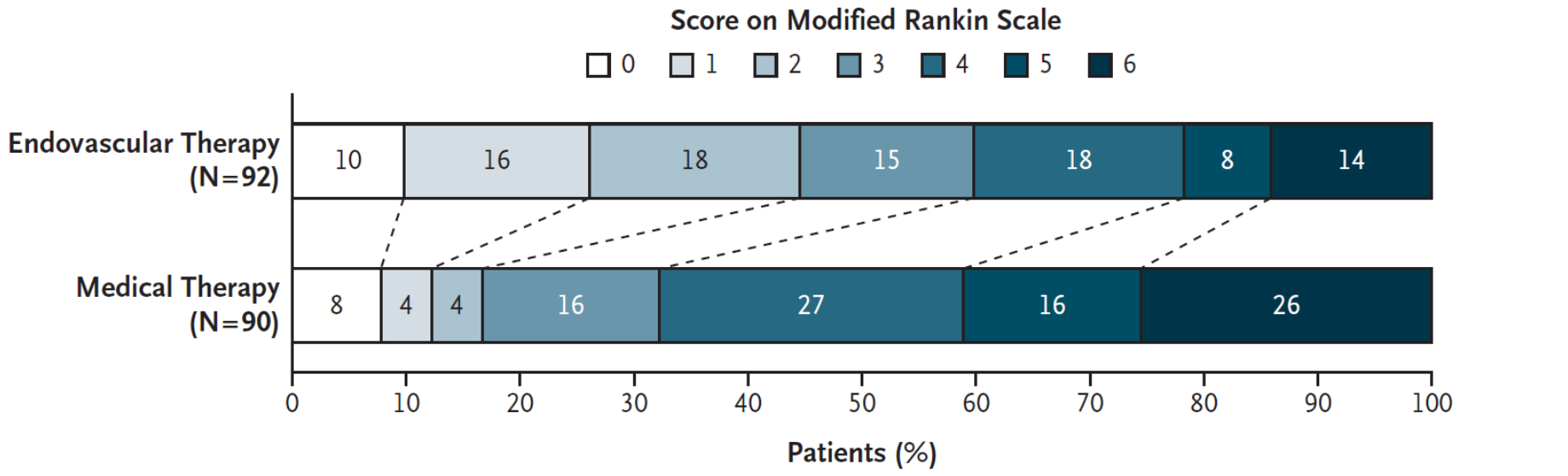


Volume of Ischemic Core, 23 ml

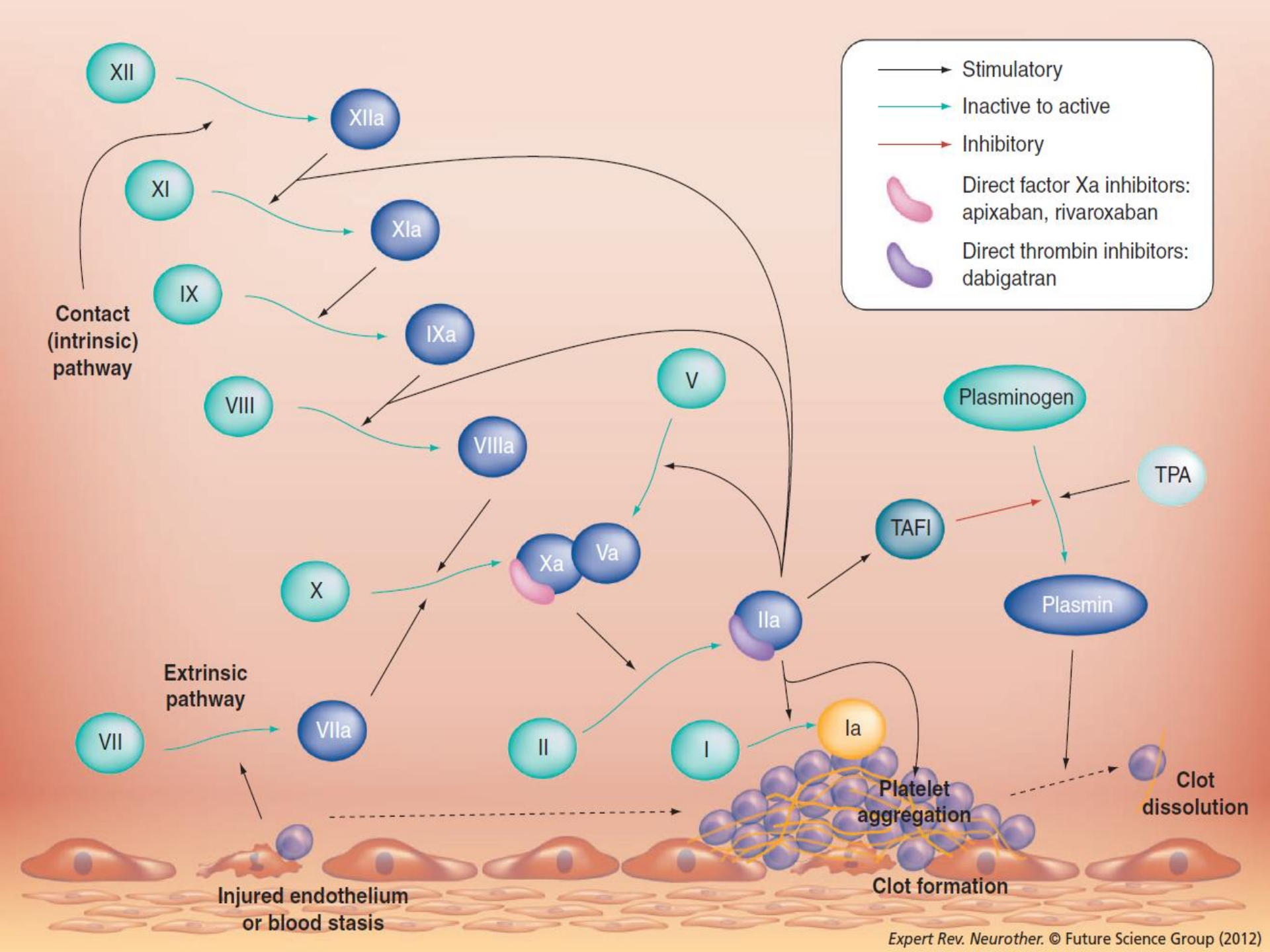
Volume of Perfusion Lesion, 128 ml

Mismatch volume, 105 ml
Mismatch ratio, 5.6

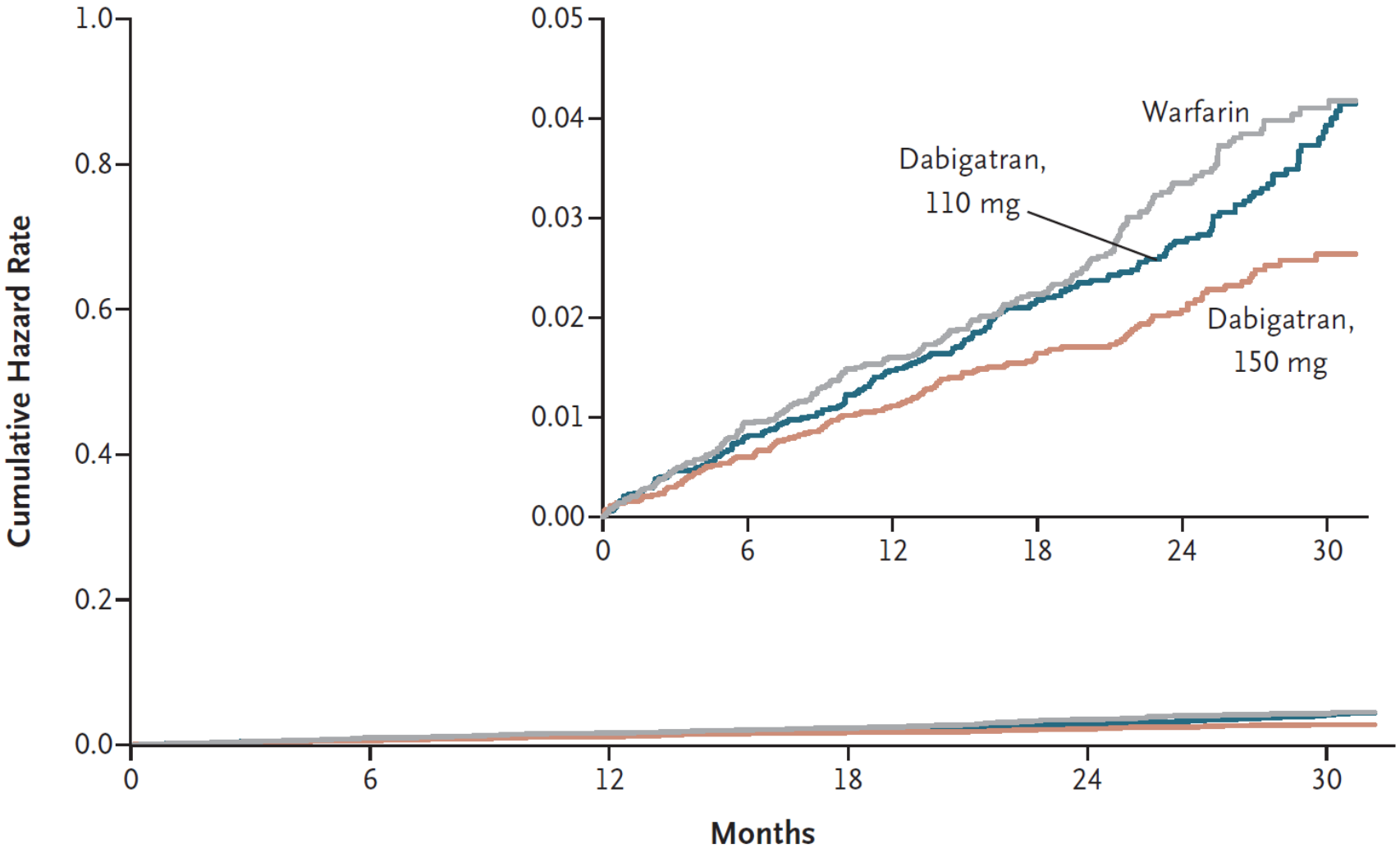
DEFFUSE-3
Albers et al. NEJM 2018; 378:708-18



Novel Oral Anticoagulants

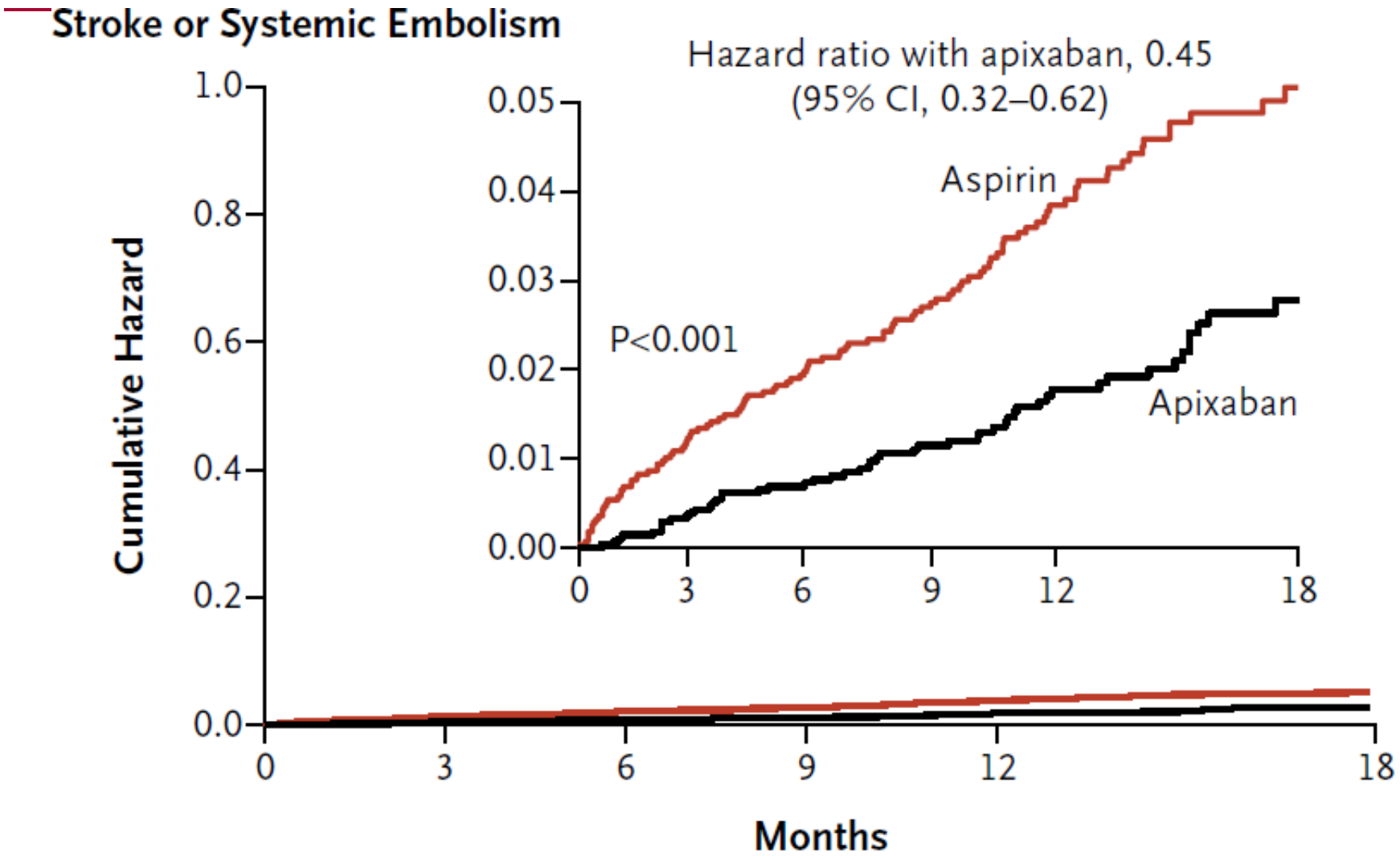


Dabigatran: Re-LY



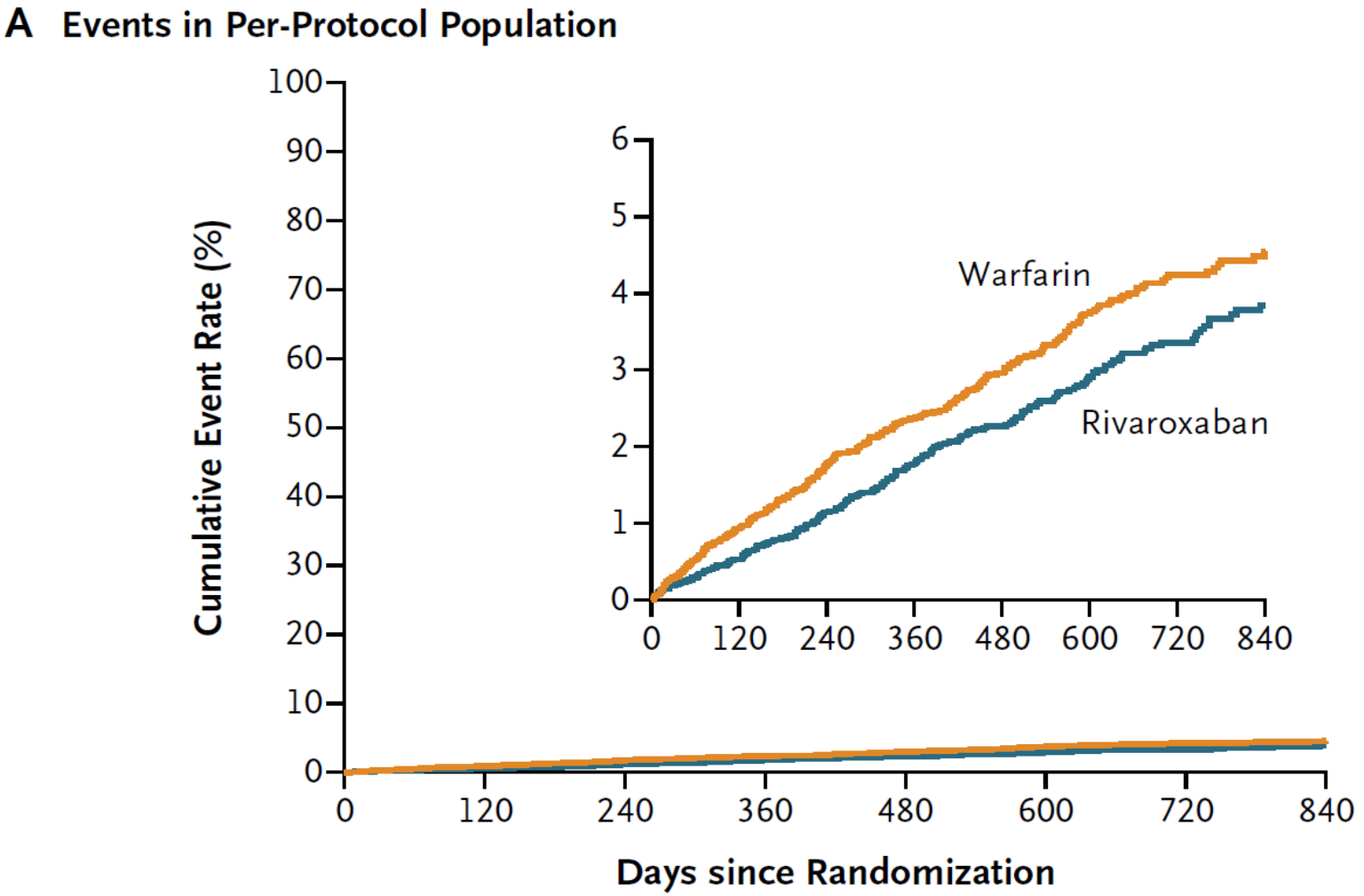
NEJM 2009; 361:2342-52

Apixaban: AVERROES



NEJM 2011;364:806-17

Rocket AF



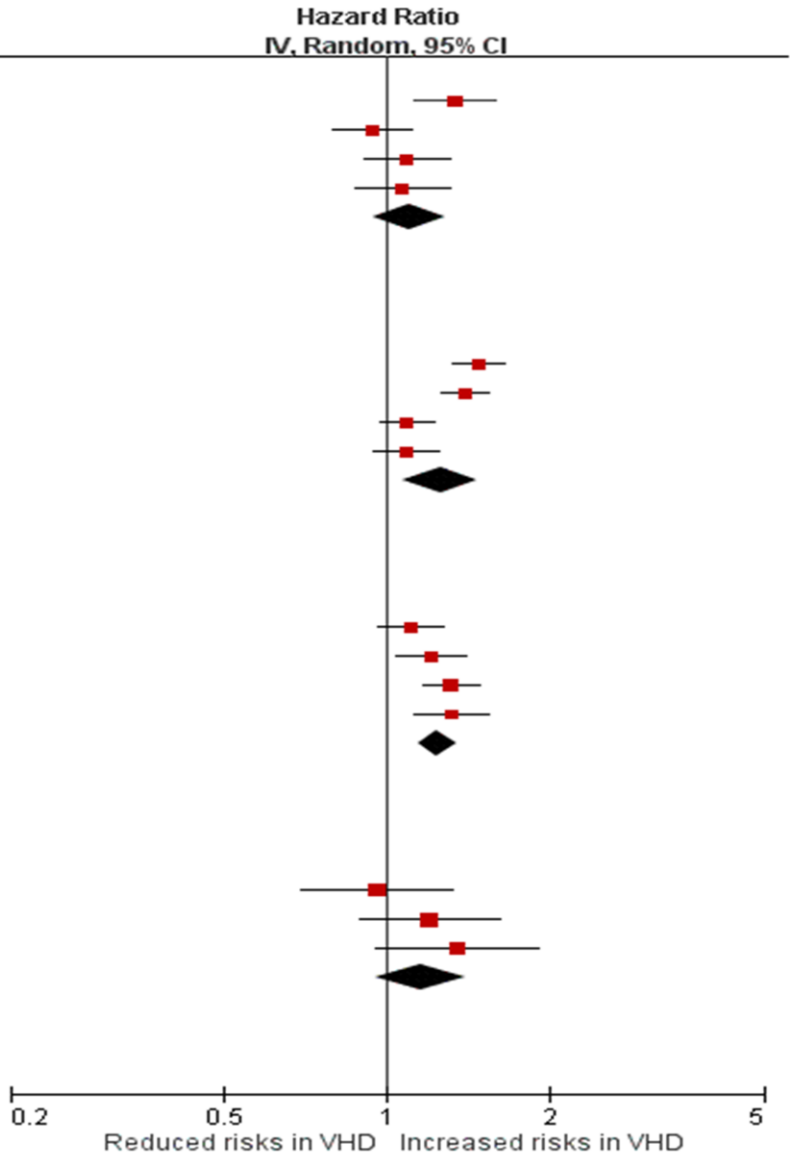
NEJM 2011; 365:883-891

No. at Risk

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
3.1.1 Stroke or systemic embolism				
ARISTOTLE[9]	0.29266961	0.08925584	25.9%	1.34 [1.12, 1.60]
ENGAGE AF[13]	-0.0618754	0.0876787	26.2%	0.94 [0.79, 1.12]
RELY[10]	0.0861777	0.09455796	24.9%	1.09 [0.91, 1.31]
ROCKET AF[11]	0.06765865	0.10448695	23.0%	1.07 [0.87, 1.31]
Subtotal (95% CI)			**100.0%**	**1.10 [0.95, 1.28]**
Heterogeneity: Tau² = 0.02; Chi² = 8.18, df = 3 (P = 0.04); I² = 63%				
Test for overall effect: Z = 1.25 (P = 0.21)				
3.1.2 All-cause mortality				
ARISTOTLE[9]	0.39204209	0.05647828	25.4%	1.48 [1.32, 1.65]
ENGAGE AF[13]	0.33647224	0.05157965	25.9%	1.40 [1.27, 1.55]
RELY[10]	0.0861777	0.05931623	25.1%	1.09 [0.97, 1.22]
ROCKET AF[11]	0.0861777	0.0716109	23.6%	1.09 [0.95, 1.25]
Subtotal (95% CI)			**100.0%**	**1.26 [1.07, 1.47]**
Heterogeneity: Tau² = 0.02; Chi² = 22.00, df = 3 (P < 0.0001); I² = 86%				
Test for overall effect: Z = 2.86 (P = 0.004)				
3.1.3 Major bleeding				
ARISTOTLE[9]	0.10436002	0.07209874	25.0%	1.11 [0.96, 1.28]
ENGAGE AF[13]	0.19062036	0.07536532	23.4%	1.21 [1.04, 1.40]
RELY[10]	0.27763174	0.06137049	31.3%	1.32 [1.17, 1.49]
ROCKET AF[11]	0.27763174	0.0827267	20.3%	1.32 [1.12, 1.55]
Subtotal (95% CI)			**100.0%**	**1.24 [1.14, 1.34]**
Heterogeneity: Tau² = 0.00; Chi² = 4.07, df = 3 (P = 0.25); I² = 26%				
Test for overall effect: Z = 5.09 (P < 0.00001)				
3.1.4 Intracranial hemorrhage				
ENGAGE AF[13]	-0.040822	0.16603184	32.9%	0.96 [0.69, 1.33]
RELY[10]	0.18232156	0.15465632	37.7%	1.20 [0.89, 1.62]
ROCKET AF[11]	0.30010459	0.17608264	29.4%	1.35 [0.96, 1.91]
Subtotal (95% CI)			**100.0%**	**1.15 [0.95, 1.40]**
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 2 (P = 0.35); I² = 4%				
Test for overall effect: Z = 1.48 (P = 0.14)				

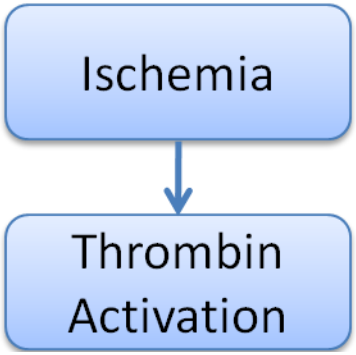
Test for subgroup differences: Chi² = 2.25 df = 3 (P = 0.52) I² = 0%



Effects of Non–Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: A Systematic Review and Meta-Analysis, Volume: 6, Issue: 7, DOI: (10.1161/JAHA.117.005835)

Thrombin toxicity

Thrombin toxicity



Thrombin toxicity

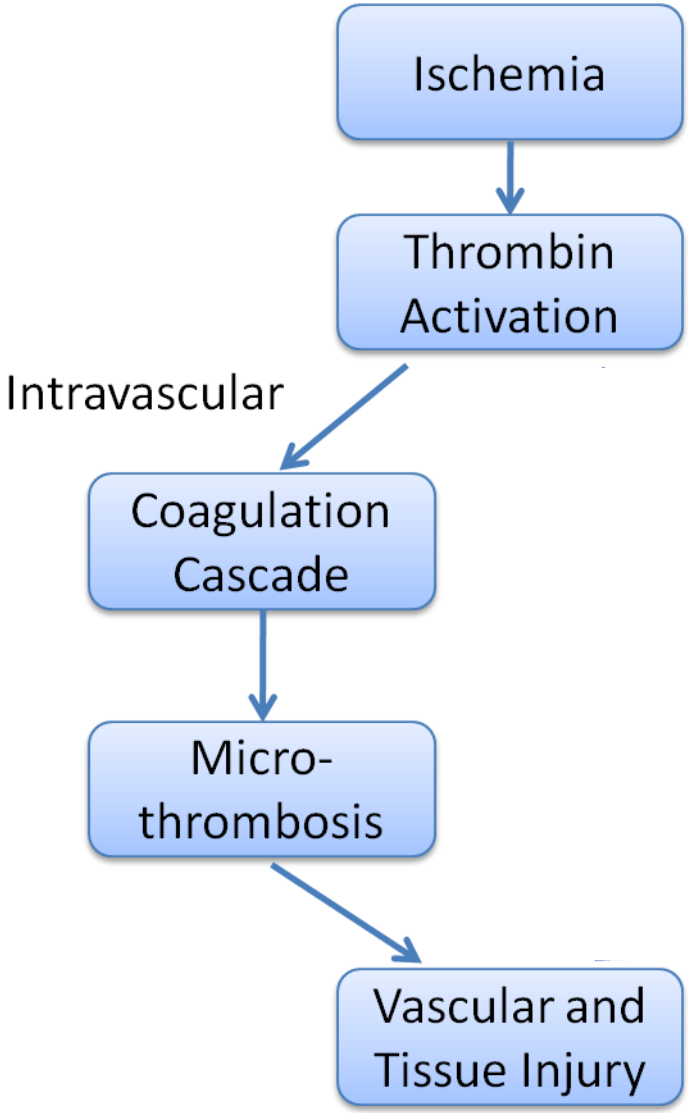
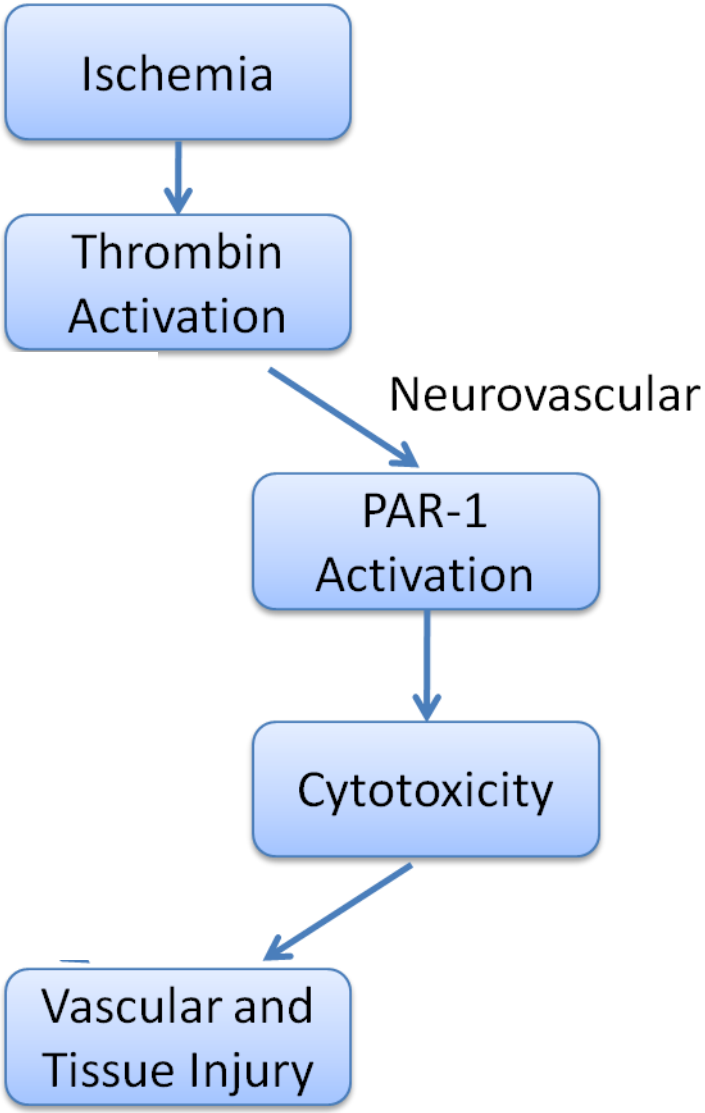


TABLE 5. Outcomes: Trials of Emergent Anticoagulation

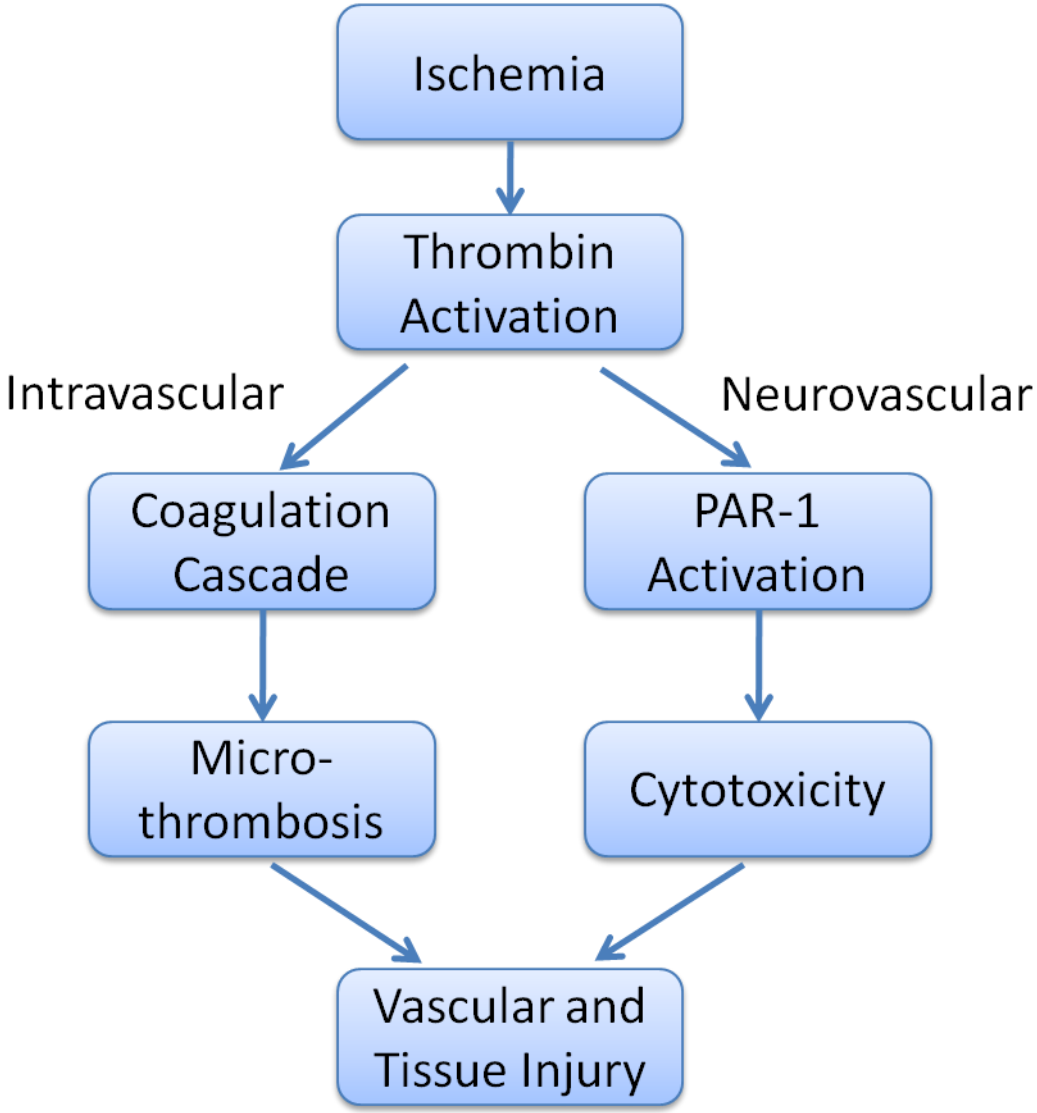
Trial	Interval	Agent	Patients Treated, N	Outcome			
				Dead, n (%)	Poor, n (%)	Good, n (%)	Excellent, n (%)
FISS	6 mo	HD nadroparin	102	13 (12.7)	32 (31.3)	...	57 (55.8)
		LD nadroparin	101	17 (16.8)	36 (35.6)	...	48 (47.5)
		Placebo	105	20 (19.0)		...	37 (35.2)
IST	6 mo	HD heparin	4856	1103 (22.7)		8 (20.3)	824 (17.1)
		LD heparin	4860			(19.6)	831 (17.3)
		Control	9718			20.1)	1641 (17.0)
TOAST	3 mo	Danaparoid				5.7)	317 (49.4)
		Placebo				7)	298 (47.0)
HAEST	3 mo					)	51 (22.8)
							48 (21.3)
							Favorable, n (%)
TAIST	6						181 (38.4)
						(51.0)	188 (38.3)
						227 (46.2)	206 (42.5)
						Unfavorable, n (%)	Favorable, n (%)
FISS-bis	6 mo					100 (40.8)	145 (59.2)
			271			116 (42.8)	155 (57.2)
			250			108 (43.2)	142 (56.8)
TOPAS	3 mo	Certoparin 3000/d	96			59 (61.5)	37 (38.5)
		Certoparin 3000 BID	97			59 (60.8)	38 (39.2)
		Certoparin 5000 BID	98			62 (63.3)	36 (36.7)
		Certoparin 8000 BID	96			54 (56.3)	42 (43.7)

See Table 1 for doses of medication prescribed to HD and LD groups.

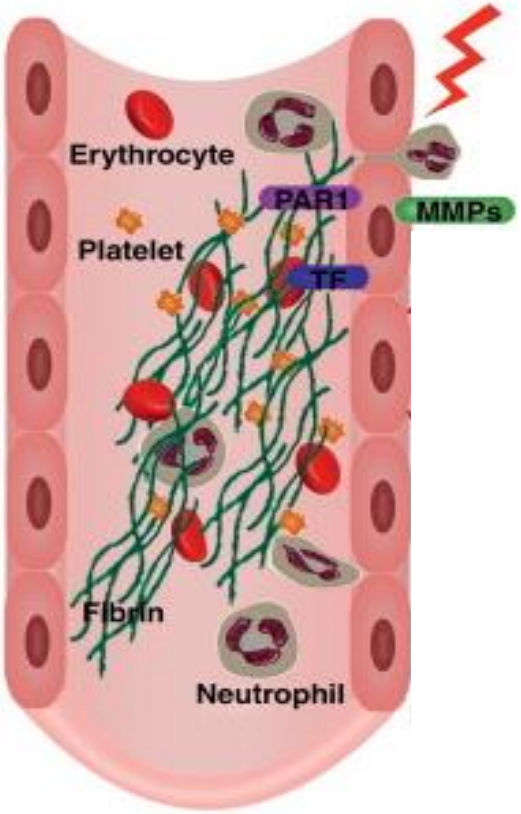
Thrombin toxicity

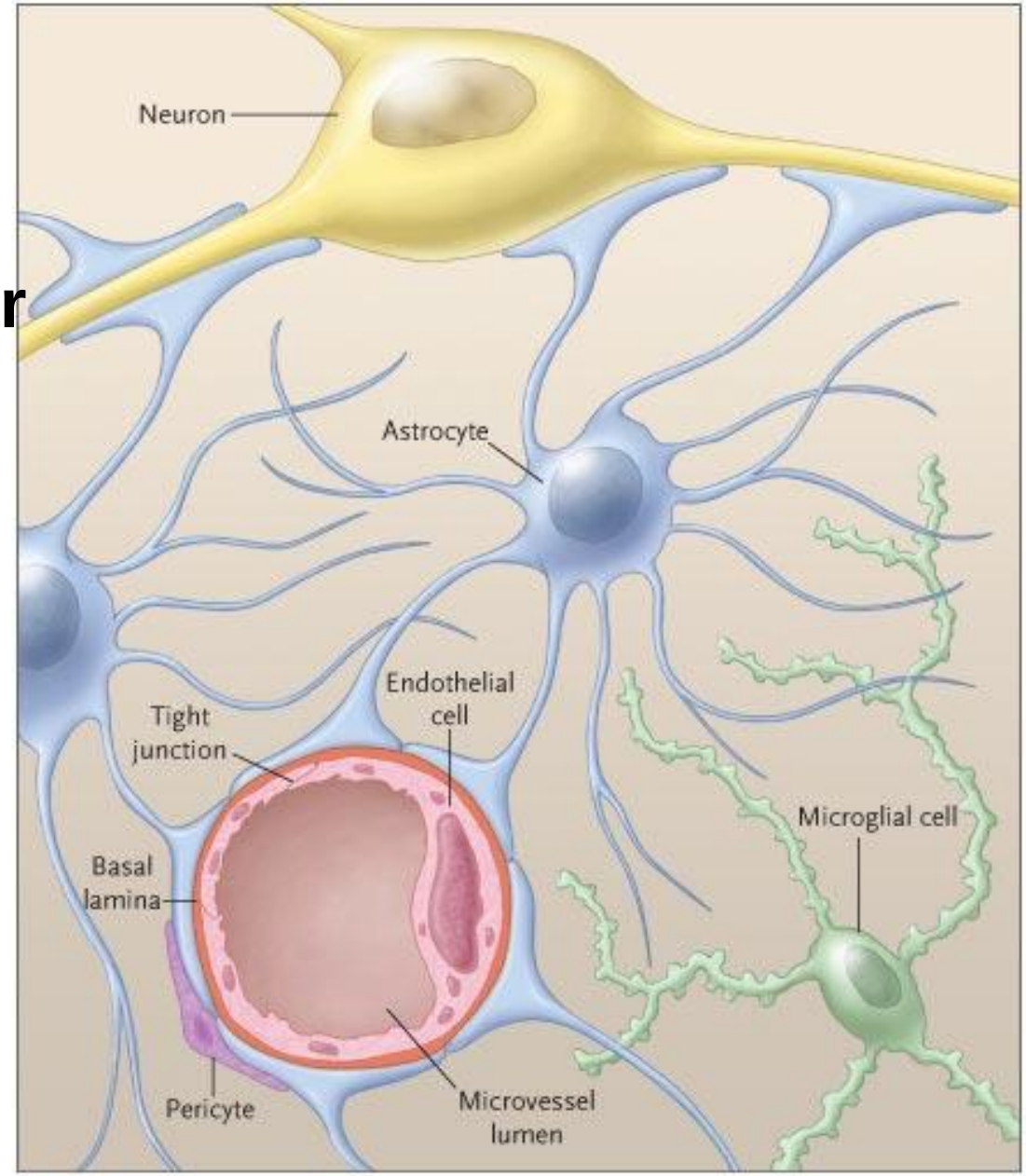


Thrombin toxicity



The Neurovascular Unit



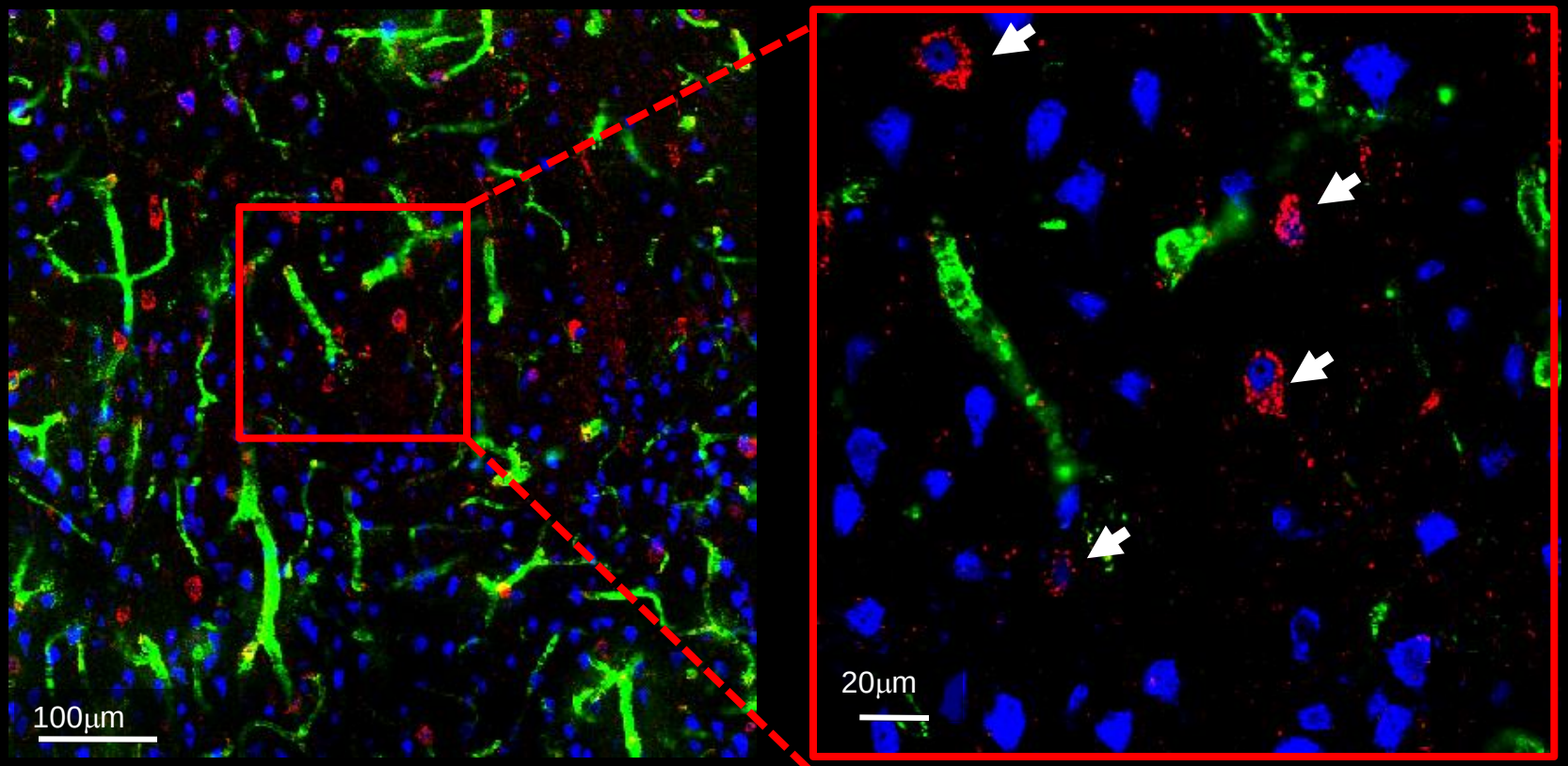


del Zoppo G. N Engl J Med 2006;354:553-555
Zhang et al. Trends inPharmacological Sci 2012;33:415

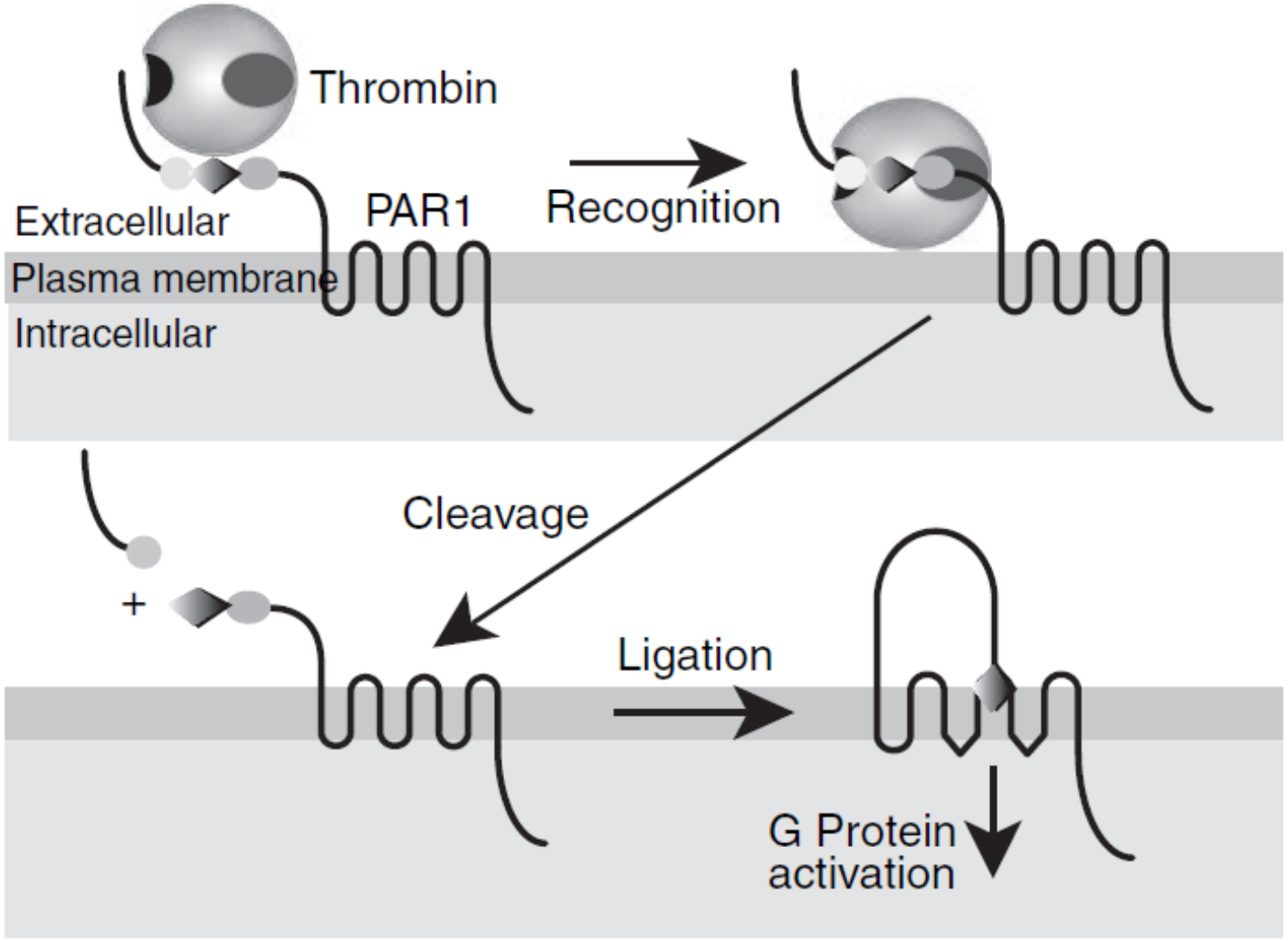
The NEW ENGLAND JOURNAL of MEDICINE

Neuronal Labeling of Thrombin

FITC-dextran
Cy3-α-NeuN
Cy5-α-thrombin



Mechanism of PAR-1 Activation



(Coughlin SR, 2005)

NeuroNEXT

The NEXT Generation of Neurologic Treatments

NIH-Network for Excellence in Neuroscience Clinical Trials

NeuroNEXT NN104 (RHAPSODY) Study

RHAPSODY

Results and Close-Out Meeting

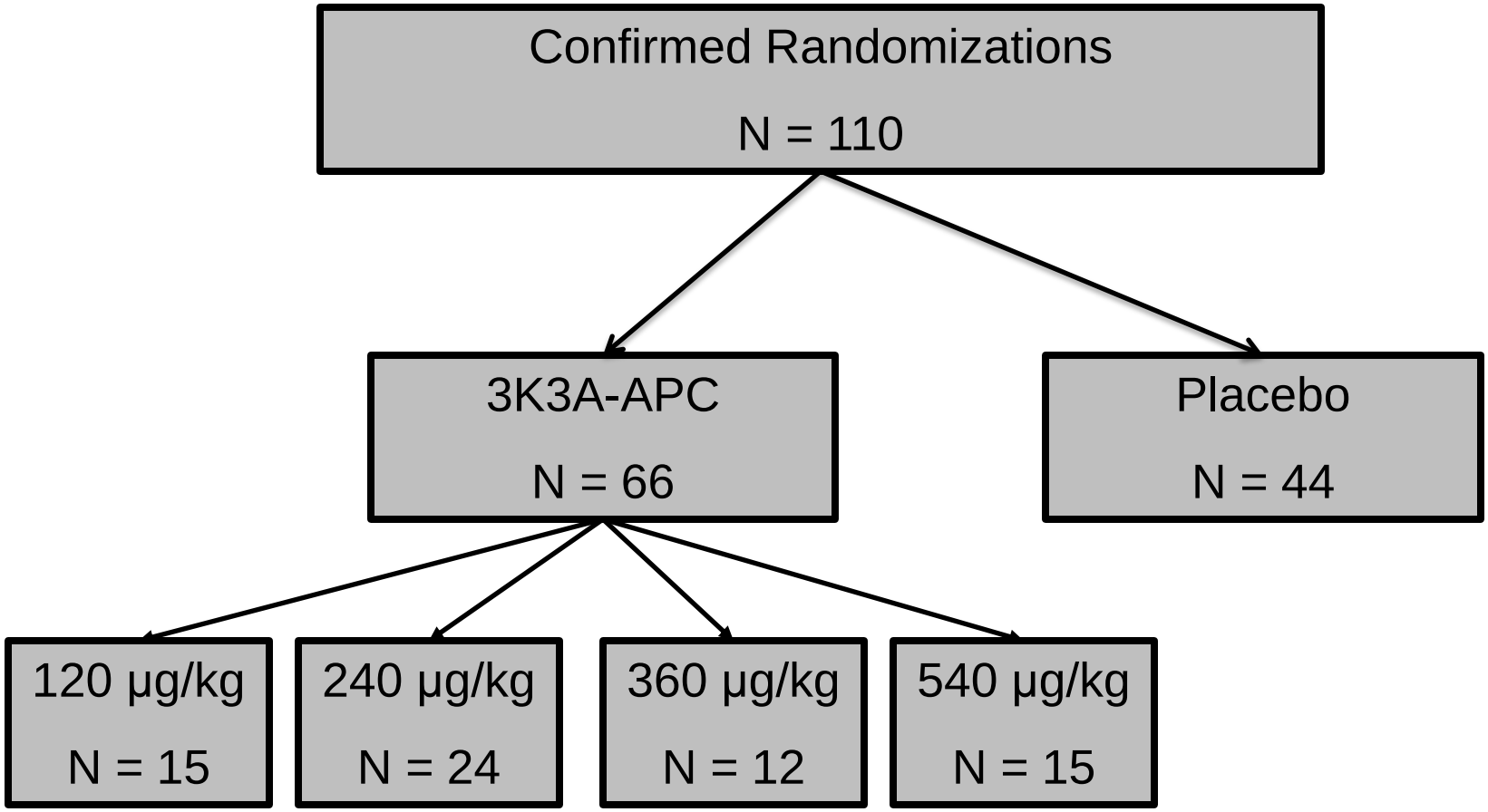
January 22nd, 2018

National Institute of Neurological Disorders and Stroke

The University of Iowa

Massachusetts General Hospital

Randomized Subjects



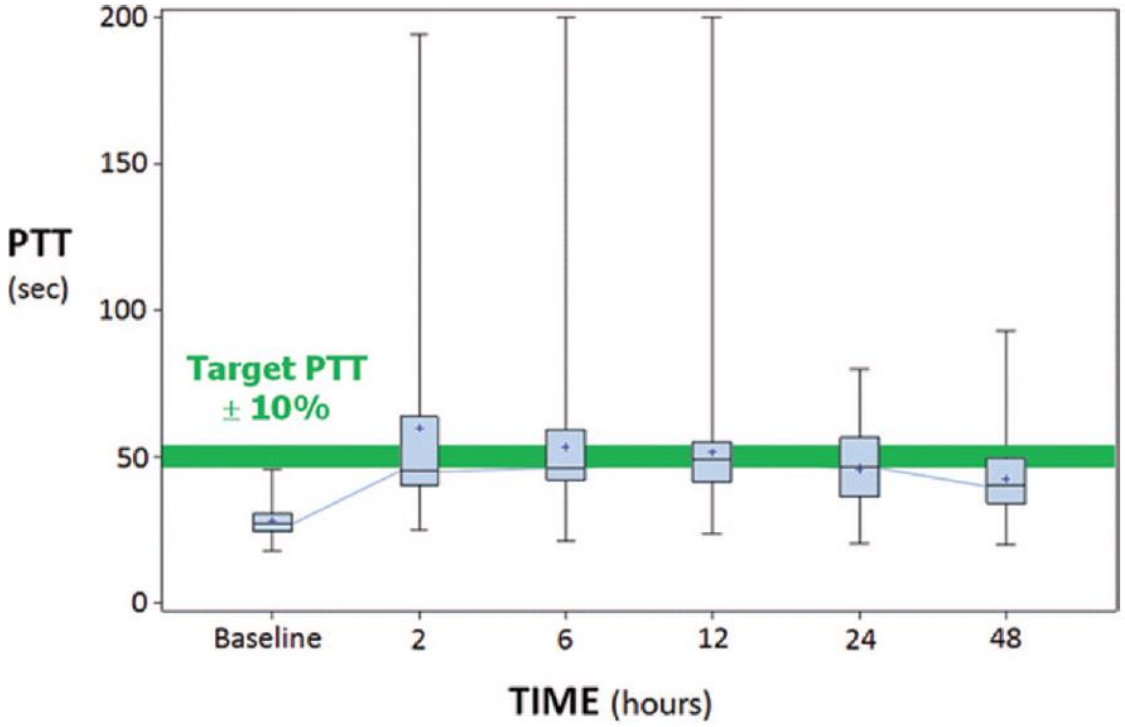
Hemorrhage

Hemorrhage Type at Day 30	Total	Dose						p-value (3K3A-APC vs. PBO)
		120 (N=12)	240 (N=16)	360 (N=6)	540 (N=9)	All 3K3A-APC (N=43)	Placebo (N=37)	
Hemorrhage (>0 mL)	61 (76.3%)	8 (66.7%)	13 (81.3%)	3 (50.0%)	5 (55.6%)	29 (67.4%)	32 (86.5%)	0.05
(>0.06 mL)	49 (61.3%)	7 (58.3%)	11 (68.8%)	2 (33.3%)	4 (44.4%)	24 (55.8%)	25 (67.6%)	0.28
(>0.5 mL)	24 (30.0%)	4 (33.3%)	5 (31.3%)	0 (0.0%)	1 (11.1%)	10 (23.3%)	14 (37.8%)	0.16
(>1.8 mL)	13 (16.3%)	1 (8.3%)	2 (12.5%)	0 (0.0%)	1 (11.1%)	4 (9.3%)	9 (24.3%)	0.07
Microbleeds	15 (18.8%)	1 (8.3%)	2 (12.5%)	3 (50.0%)	1 (11.1%)	7 (16.3%)	8 (21.6%)	0.54
Total Hemorrhage Volume						0.8±2.1	2.1±5.8	0.07

Hemorrhage

Hemorrhage Type at Day 30	Total	Dose						p-value (3K3A-APC vs. PBO)
		120 (N=12)	240 (N=16)	360 (N=6)	540 (N=9)	All 3K3A-APC (N=43)	Placebo (N=37)	
Hemorrhage (>0 mL)	61 (76.3%)	8 (66.7%)	13 (81.3%)	3 (50.0%)	5 (55.6%)	29 (67.4%)	32 (86.5%)	0.05
(>1.8 mL)	13 (16.3%)	1 (8.3%)	2 (12.5%)	0 (0.0%)	1 (11.1%)	4 (9.3%)	9 (24.3%)	0.07
Total Hemorrhage Volume						0.8±2.1	2.1±5.8	0.07

ARTS: Barreto, Alexandrov, Lyden, et al
Stroke. 2012;43:00

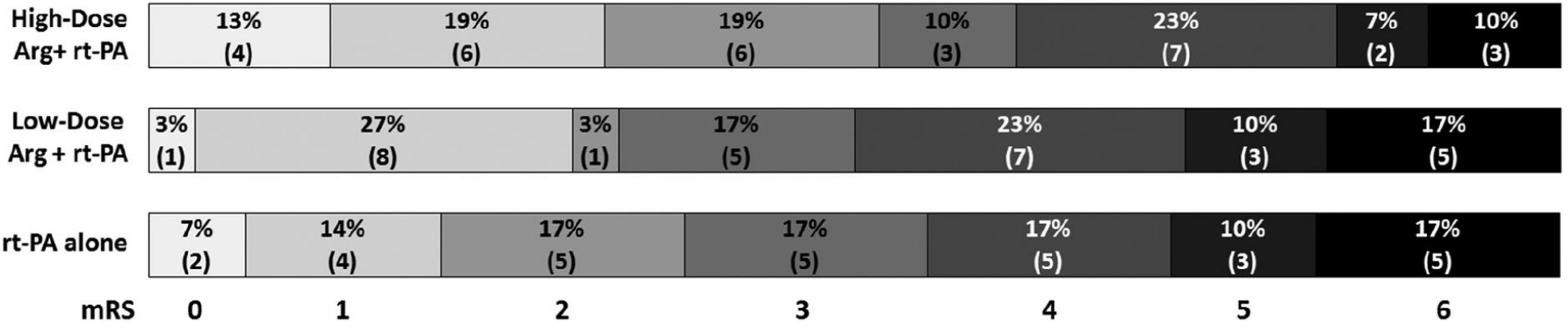


tPA plus Argatroban
100mcg/kg
Target PTT 1.75x

sICH in 3 (4.6%)

Early recanalization
In 61%

ARTSS-2
Barreto et al. Stroke. 2017;48:1608-1616



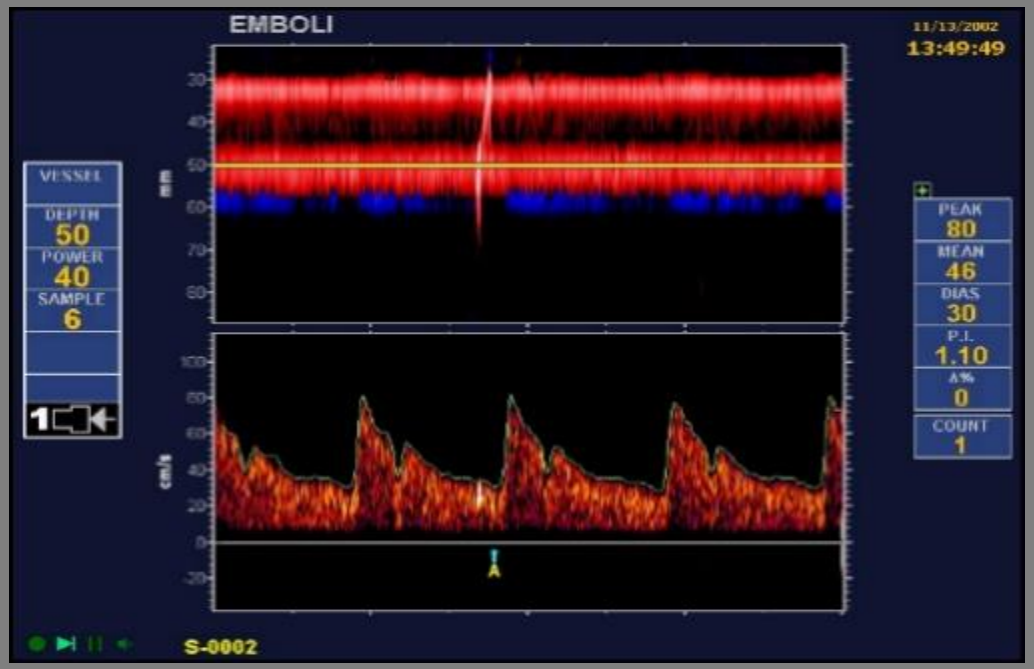
To be tested in upcoming MOST trial

“Truth does not change because it is, or is not, believed by a majority of the people.”


Thank you

New Uses for Transcranial Doppler Monitoring

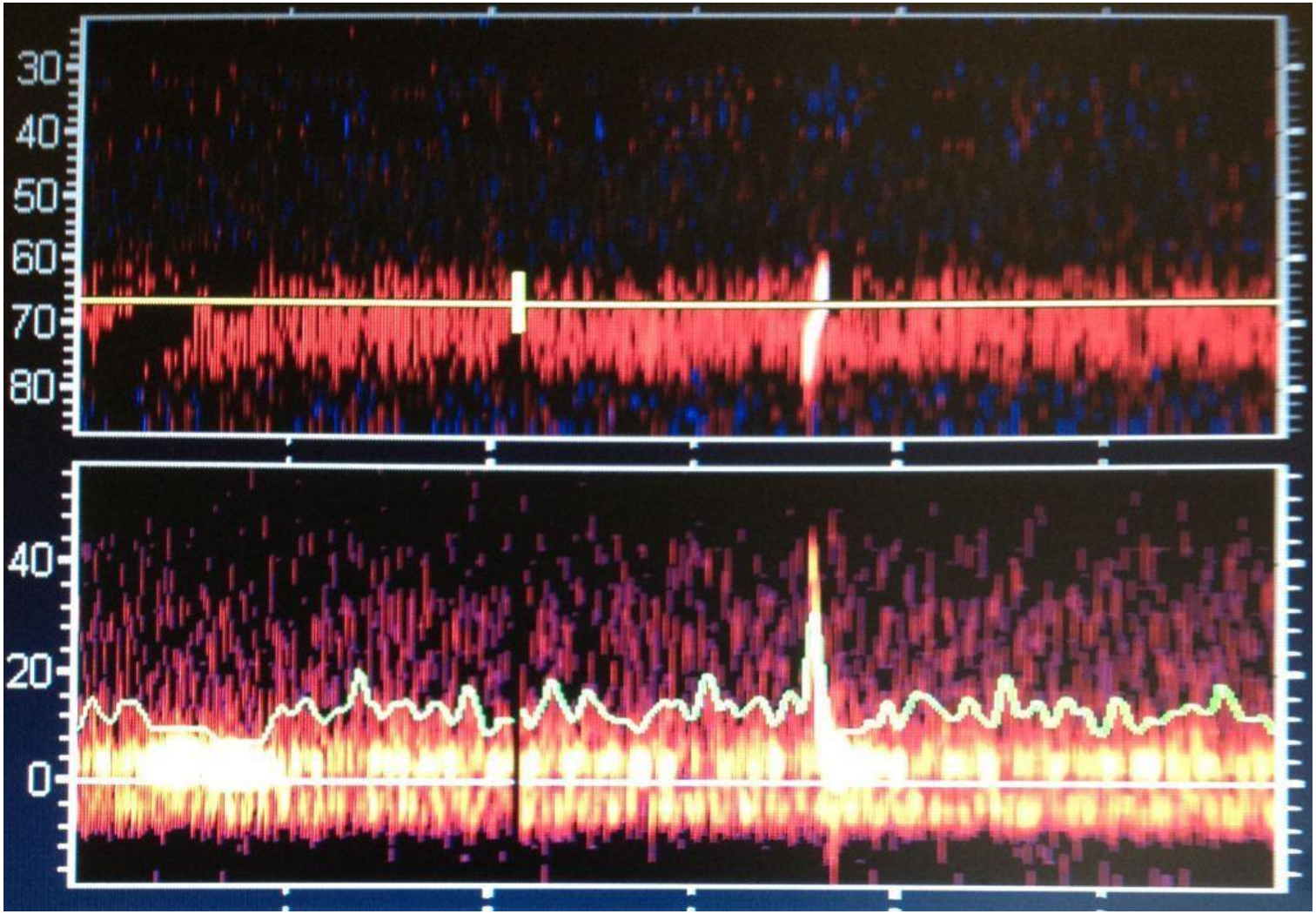
Intracranial Emboli Detection



New Indications

- Detection of Patent Foramen Ovale
- Emboli Detection
- Intra-operative monitoring

High Intensity Transients (HIT)

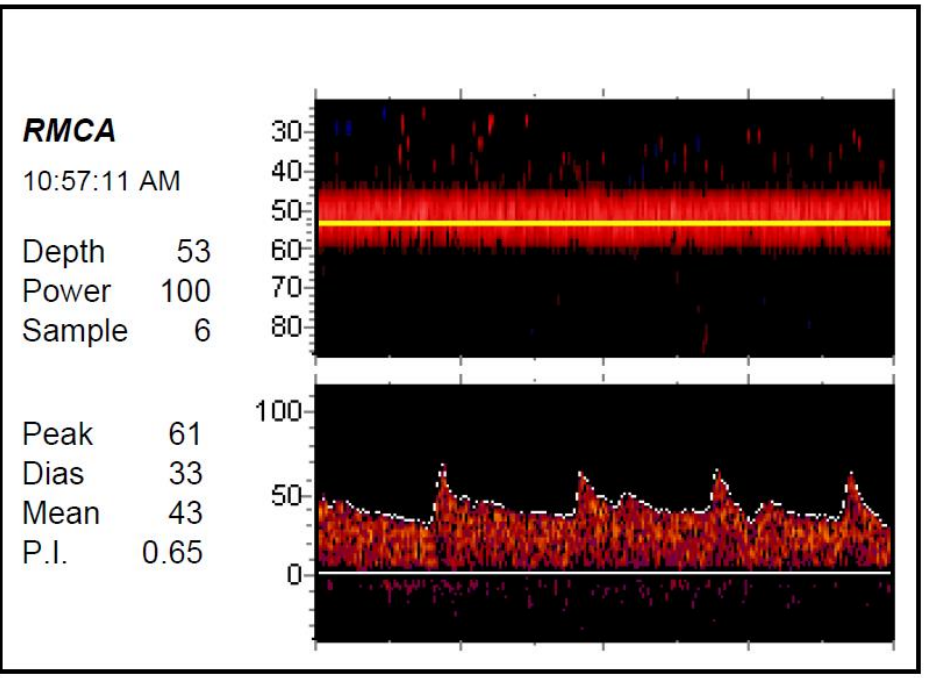


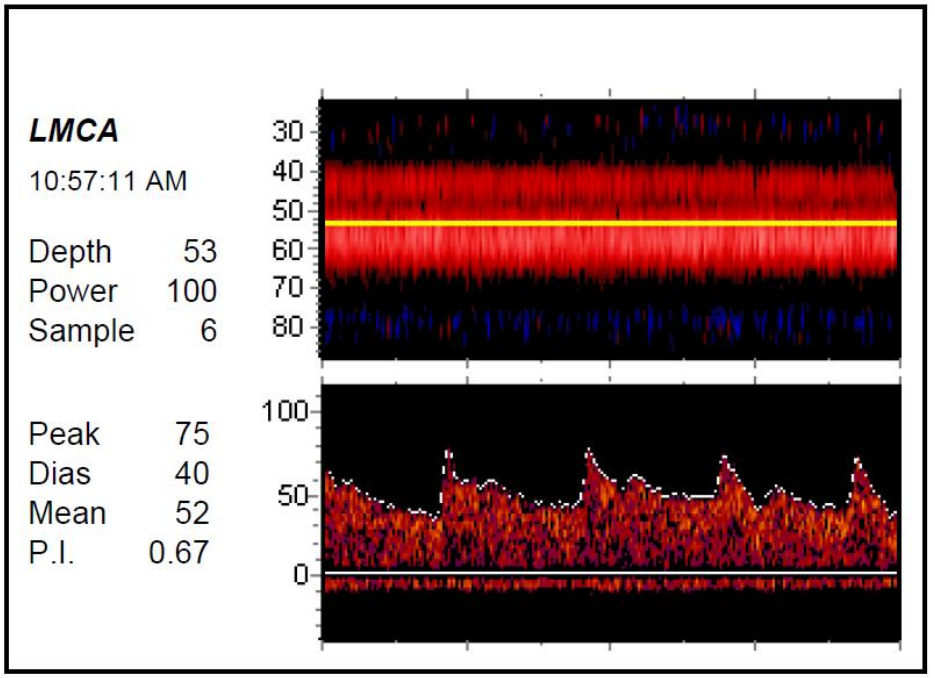
Detection of PFO

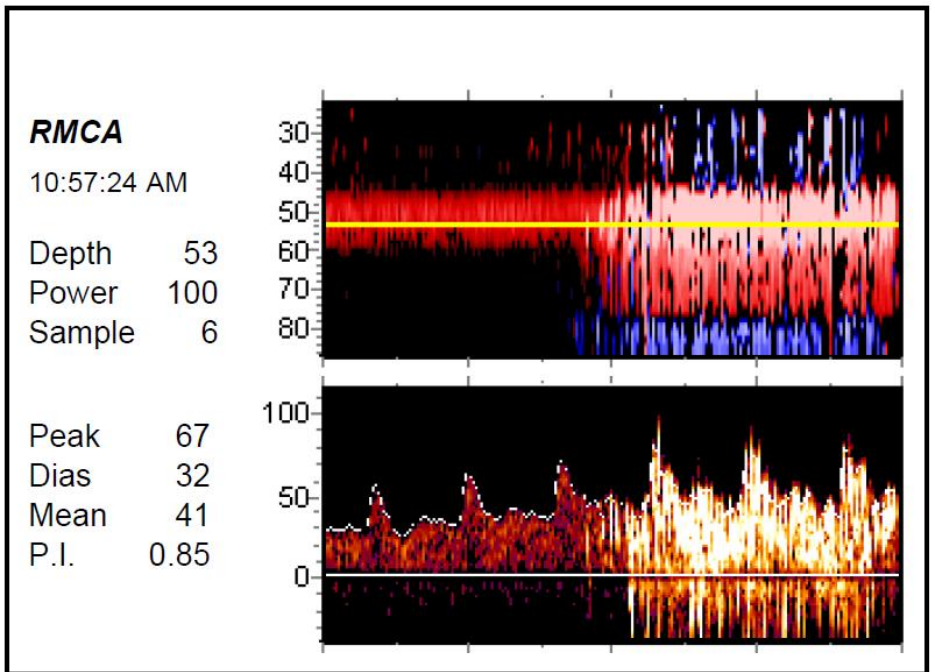
- **TCD superior to TTE with bubbles**
  - Sensitivity 68% vs 47%
  - Di Tullio, Sacco et al. Stroke 1993;24:1020-1024

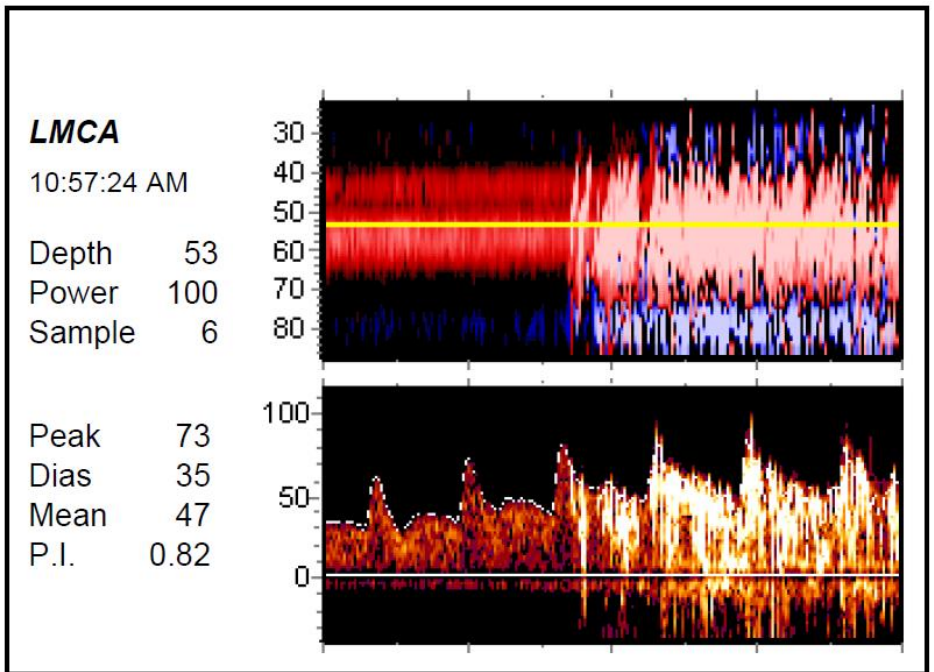
- **Contrast TCD superior to contrast TEE**
  - Sensitivity 75% vs 48% without Valsalva
  - Both 100% with Valsalva
  - Caputi, Carriero et al. J. Stroke Cerebrovascular Dis. 2009;18:343-348

- All 3 are somewhat operator dependent


RMCA
10:57:11 AM
Depth 53
Power 100
Sample 6
Peak 61
Dias 33
Mean 43
P.I. 0.65
30
40
50
60
70
80
100
50
0


LMCA
10:57:11 AM
Depth 53
Power 100
Sample 6
Peak 75
Dias 40
Mean 52
P.I. 0.67
30
40
50
60
70
80
100
50
0


RMCA
10:57:24 AM
Depth 53
Power 100
Sample 6
Peak 67
Dias 32
Mean 41
P.I. 0.85
30
40
50
60
70
80
100
50
0


LMCA
10:57:24 AM
Depth 53
Power 100
Sample 6
Peak 73
Dias 35
Mean 47
P.I. 0.82
30
40
50
60
70
80
100
50
0

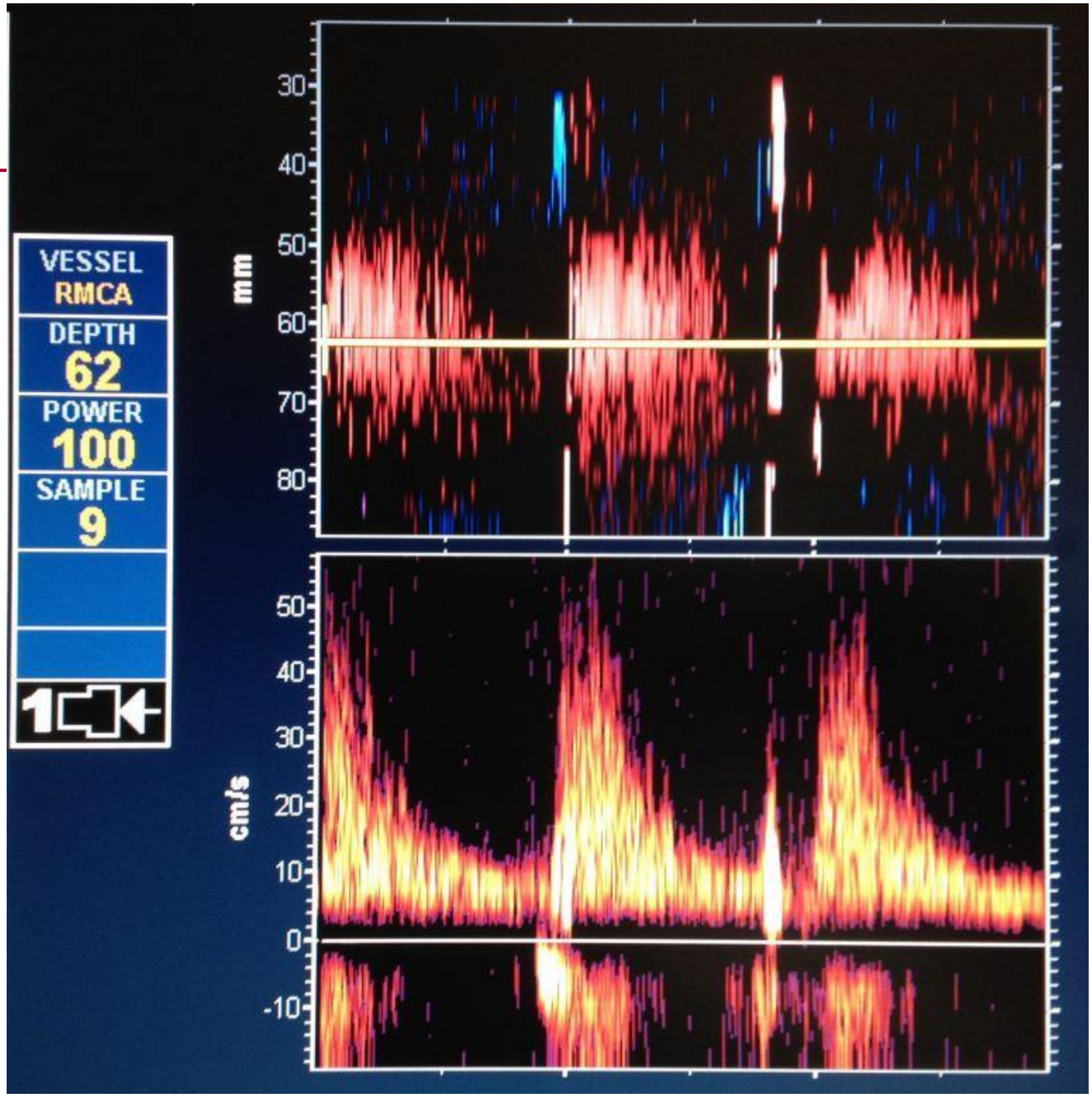
25 patient studies

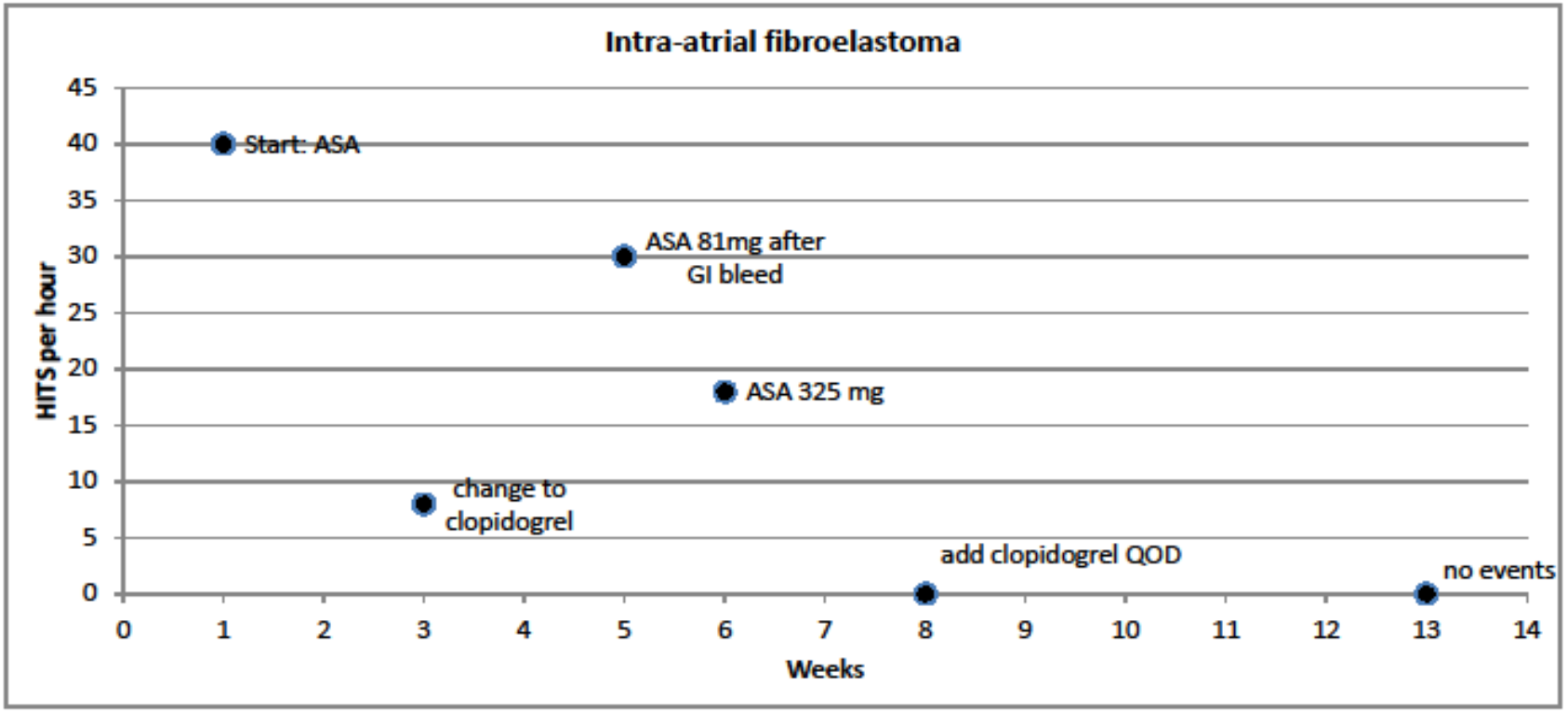
8 positive for PFO

Of those 8, 2 were NEGATIVE on TTE

All confirmed on angio

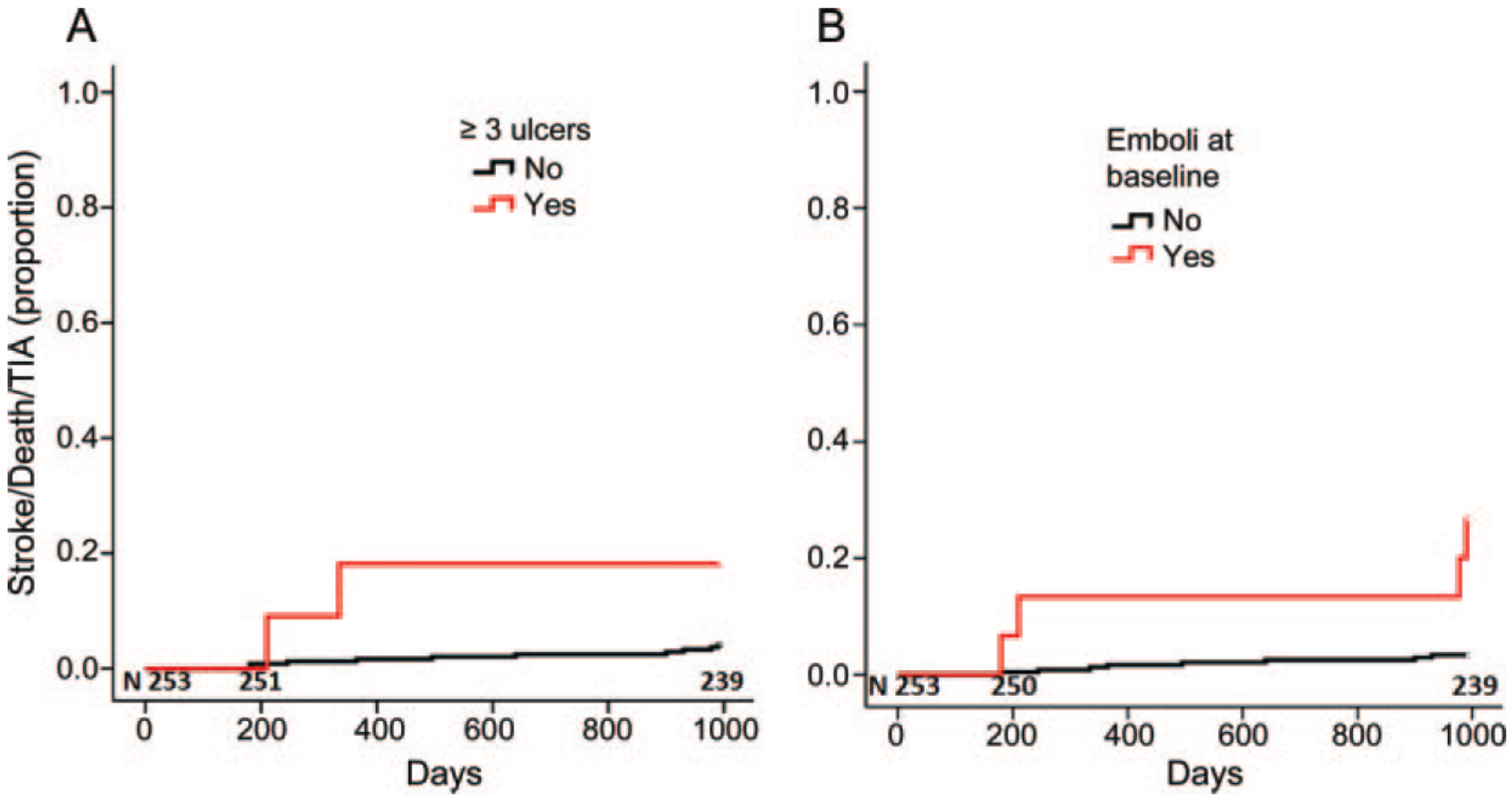
Emboli Detection




Intra-atrial fibroelastoma
HITS per hour
45
40
35
30
25
20
15
10
5
0
Start: ASA
ASA 81mg after GI bleed
ASA 325 mg
change to clopidogrel
add clopidogrel QOD
no events
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Weeks

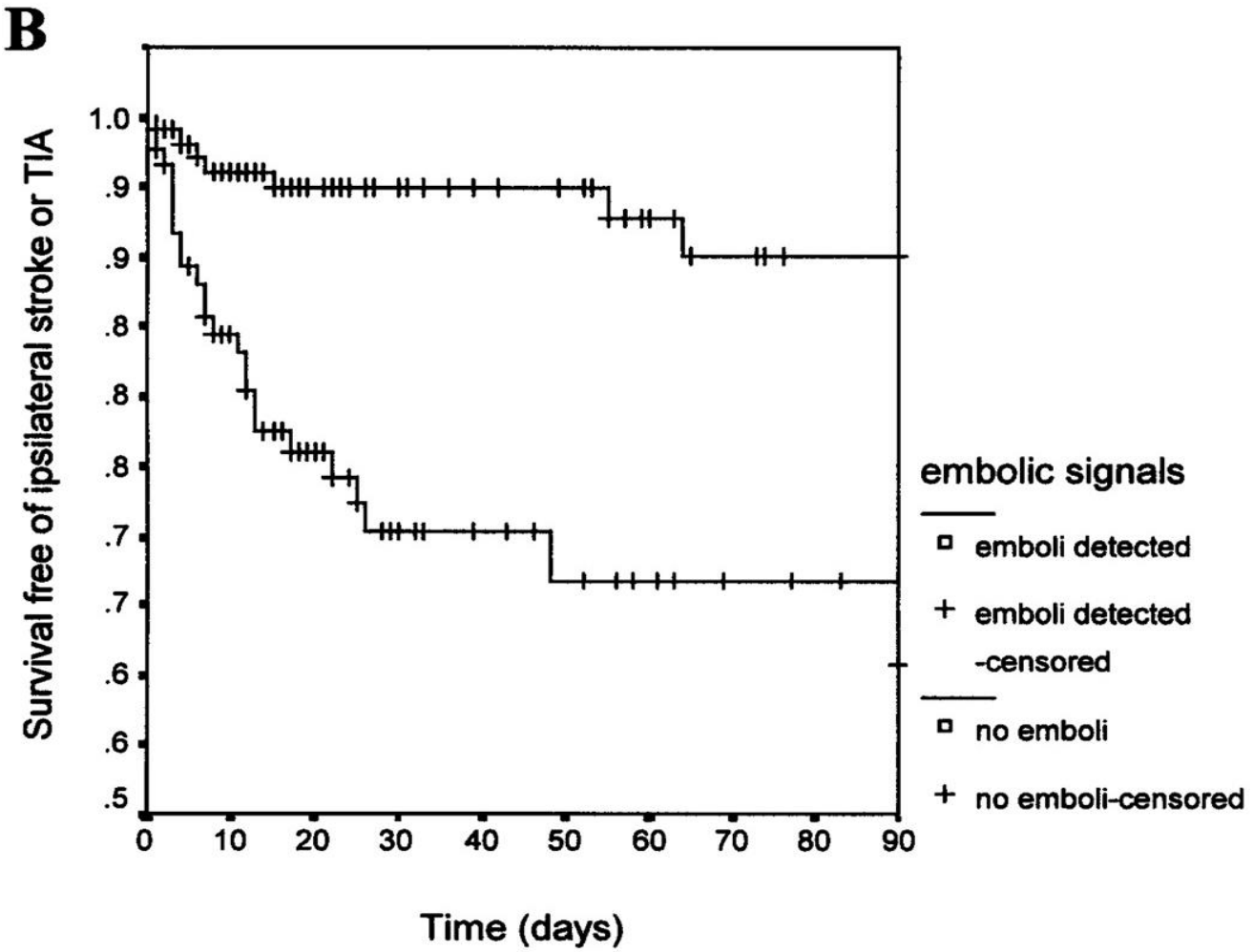
Risk of stroke with Asymptomatic Carotid Stenosis

Figure 2 Kaplan-Meier survival by baseline status



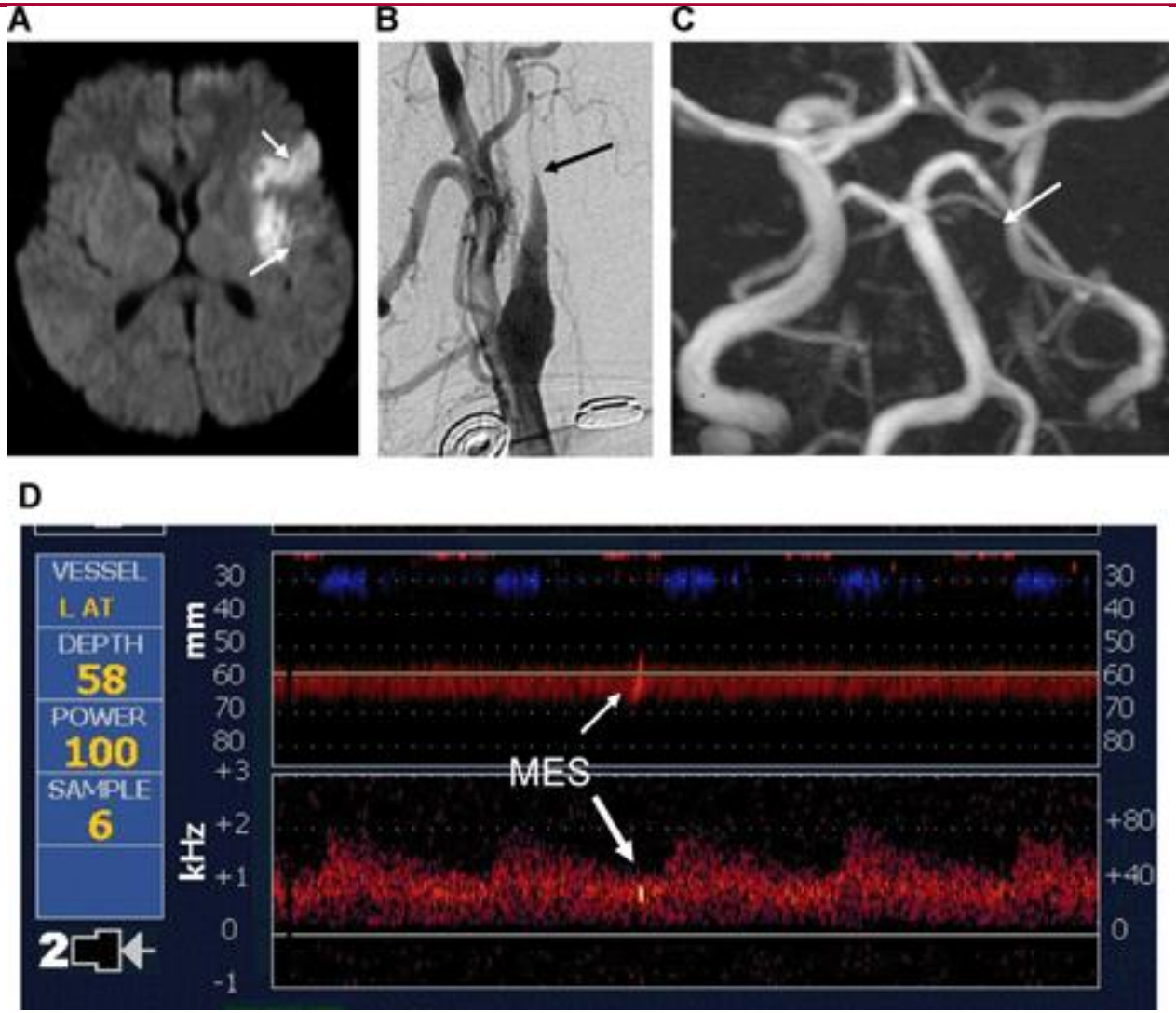
 Madani, Beletsky. Neurology 2011;77:744-750

Risk of stroke with Symptomatic Carotid Stenosis

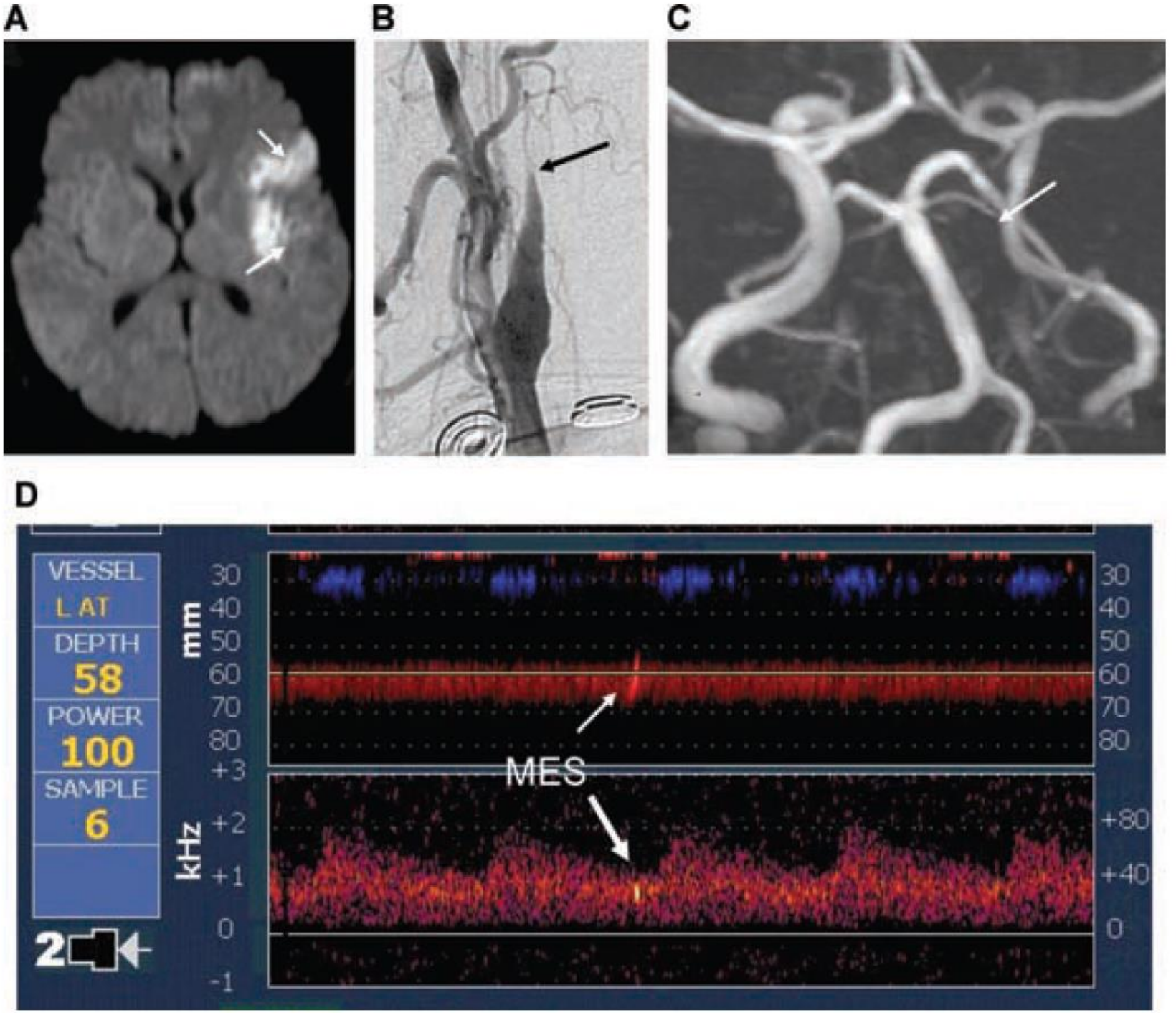


 Stroke. 2005; 36: 971-975

Transcranial Doppler Microembolic Signal Monitoring is Useful in Diagnosis and Treatment of Carotid Artery Dissection: Two Case Reports



Journal of Neuroimaging
Volume 17, Issue 4, pages 350-352, 4 SEP 2007


A
B
C
D
VESSEL
L AT
DEPTH
58
POWER
100
SAMPLE
6
2
mm
30
40
50
60
70
80
kHz
+3
+2
+1
0
-1
MES
+80
+40
0

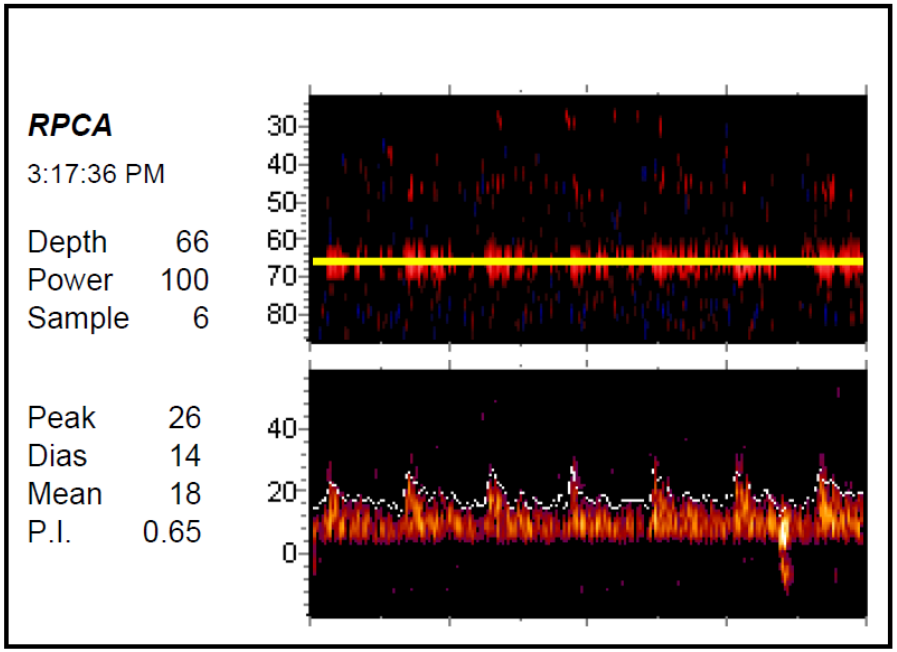
Case

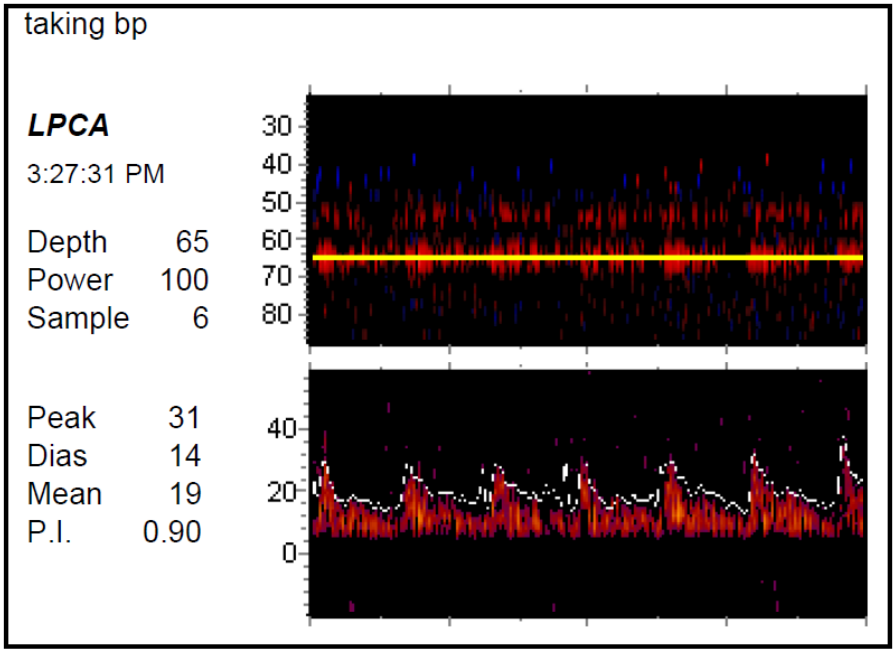
- 61 yo former pro bass fisherman
- Several episodes dizzy, diplopia, all resolved
- Most recent spell treated in ED with nitro paste and benadryl
- PMD treated with steroids
- 3 days later returned to ED with same sx
  - CT scan showed bilateral cerebellar strokes
- Referred to Cedars-Sinai urgently

More history…

- 3 months prior was seen for acute stroke: vertigo and hemi-body numbness
- Transferred to a tertiary facility
- Added asa to his plavix
- CTA said to show occluded left vertebral artery

Initial TCD



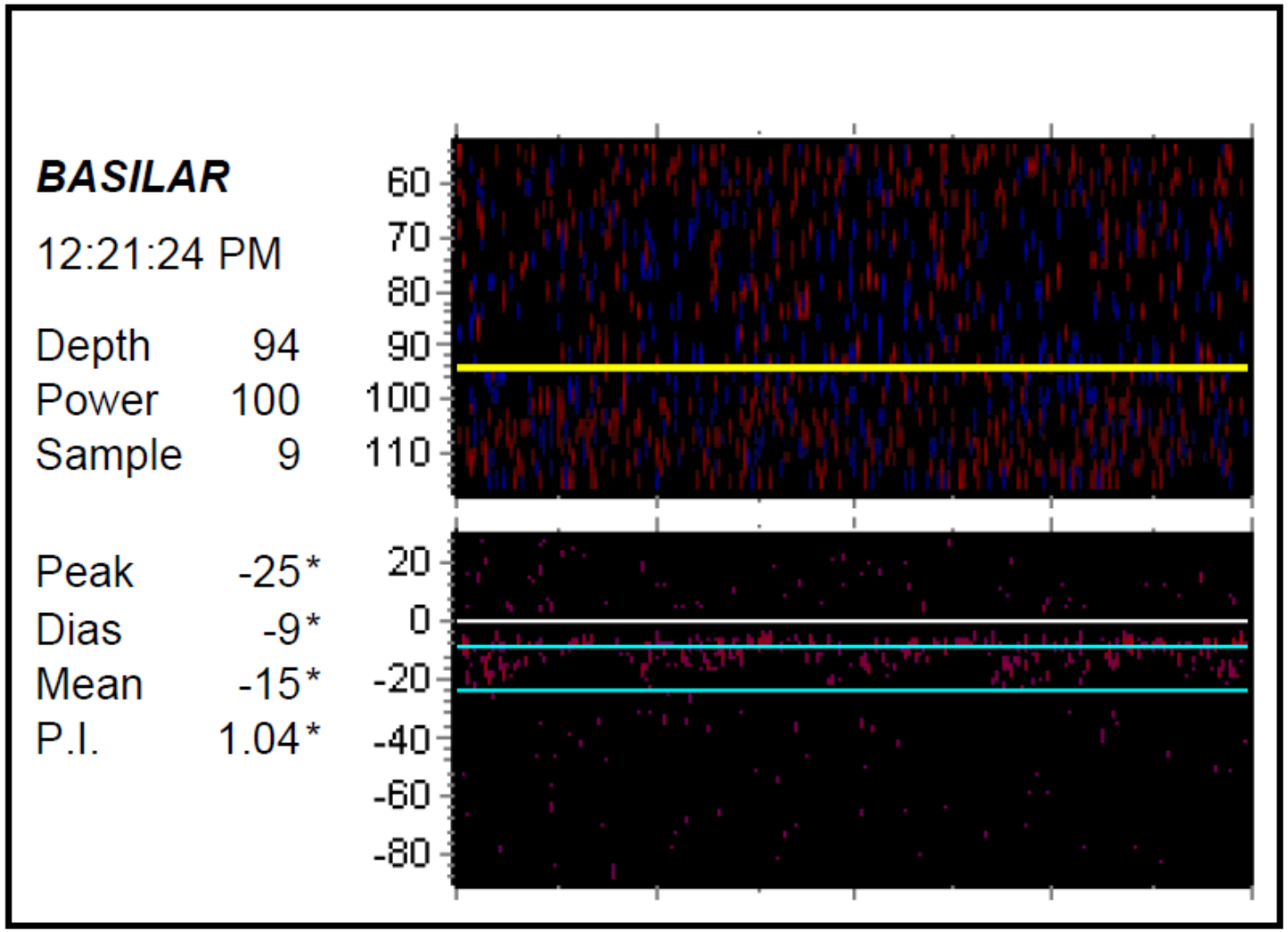


30 HITS right PCA, none in the left

Titrate anti-thrombotic therapy

- Since he was having HITS on ASA and Plavix we changed to prasugrel
- TCD one week later showed 9 HITS so we added aggrenox
- One month later, no sx but repeat TCD “artifact laden”
- Two months later, repeat TCD: no HITS
- One year after initial strokes, no HITS so we stopped aggrenox
- Two years after stroke, still has occluded vert and low basilar flow:
- No strokes

Titrate anti-thrombotic therapy



Thank You