

Current and Near-term Impact of Biomarkers for Stroke

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IOM Neuroscience Forum
Workshop on Biomarkers and Biosignatures
February 26, 2007

Acute Ischemic Stroke Therapy

- One acute therapy (11 yrs ago; 2% of strokes)
- > 100 failures
- Disconnect between laboratory successes and clinical trials
- Near-term potential for biomarker impact: high

Current and Near-term Impact of Biomarkers for Stroke

Summary recommendation

- MRI markers for patient selection, dose finding, evidence for drug activity
- Increasing recognition as important
- Emerging in Phase II trials
 - Disparate efforts to establish data sharing
 - Thousands of patients (raw data) available

Current and Near-term Impact of Biomarkers for Stroke

Summary recommendation

- Needs
 - Pooling of clinical trial and academic data
 - Standards of acquisition and processing
 - refine penumbra (at-risk, salvageable) definition
 - Standardization of selection and outcome definitions and validation

What is different about acute stroke?

- § Emergency diagnosis

 - § Prone to increased error

- § Reliance on clinical impression only

 - § no objective (central) confirmation of dx or outcome

- § Meaningful outcomes are disability scales

 - § no expert consensus on which scale, cut-point, or statistical approach

What is different about acute stroke?

§ Single event

§ not progressive

§ Clinically meaningful pathology is macroscopic – the infarct

§ Biomarker (infarct) is the final pathological step responsible for clinical effects

Current and Near-term Impact of Biomarkers for Stroke

Summary recommendation

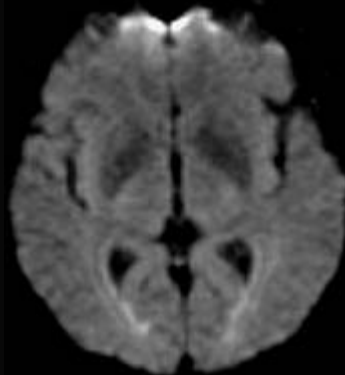
- Acute ischemic stroke therapy development
 - MRI markers for
 - Patient selection
 - establish diagnosis (e.g., focal ischemia, lesion)
 - target appropriate patients (e.g., penumbra)
 - Pathologically relevant outcomes
 - Reperfusion, infarct volume
 - Dose selection

If stroke is the target, then select patients with confirmed stroke

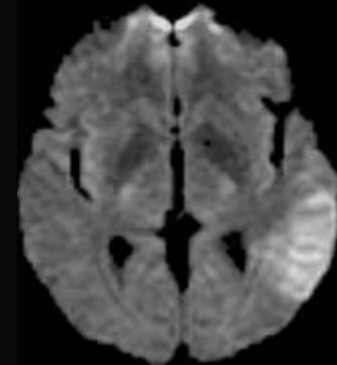
Perfusion



Not
Diffusion-
Weighted



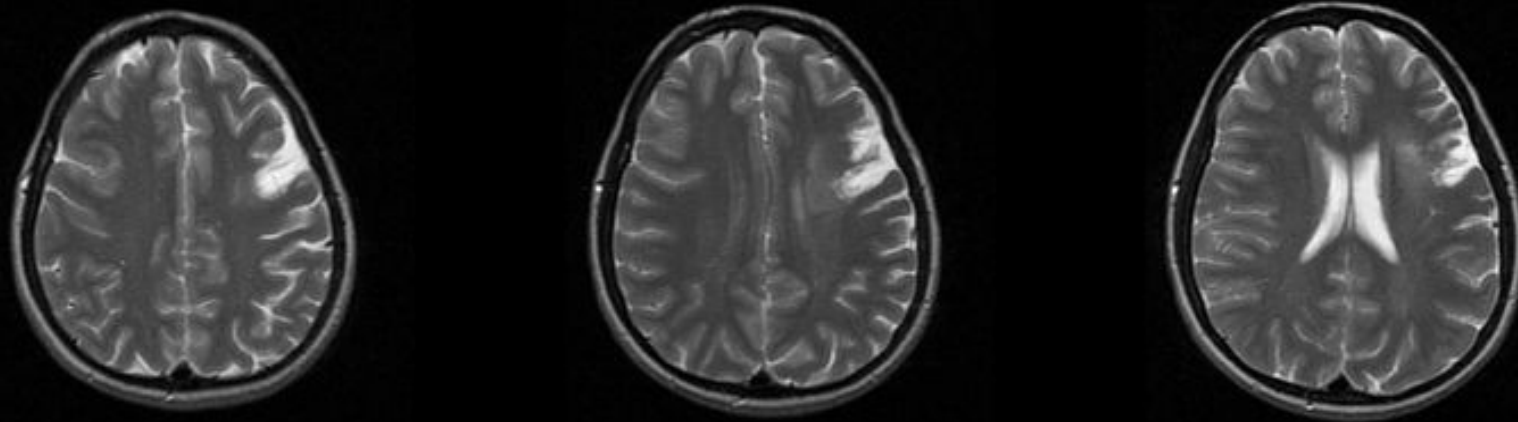
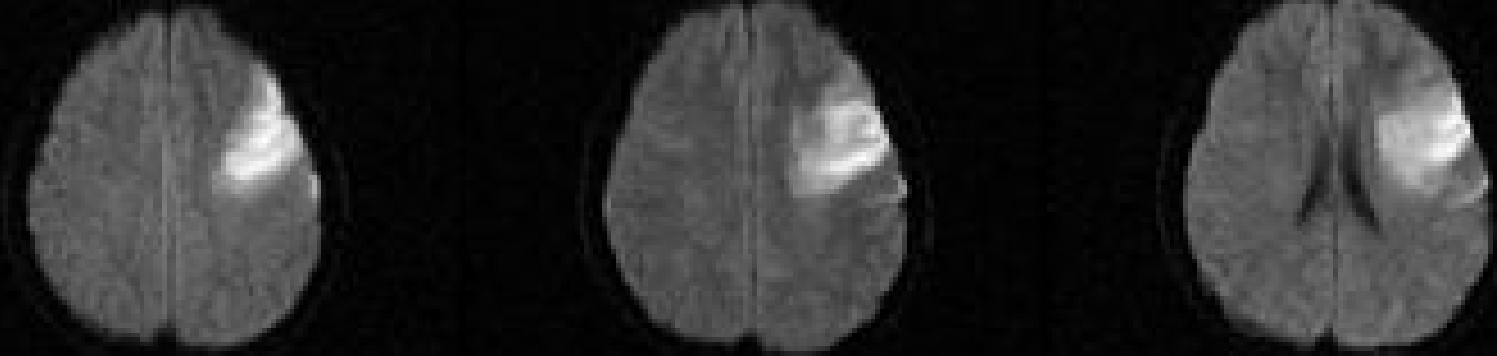
Not
Diffusion-
Weighted



Acute ischemic injury is dynamic and potentially reversible

Acute Stroke: Diffusion Weighted MRI

Lesion Volume = 62 cc



Chronic Stroke: T2-Weighted MRI

Lesion Volume = 17 cc

Lesion Volume as Marker of Therapeutic Effect

In animal models, lesion volume reduction is both necessary and sufficient evidence of target therapeutic effect (for neuroprotective or lytics)

Replicating preclinical evidence in the clinic is possible !

Questions in clinical trial design

Dosing regimen?

Plasma levels?

Drug reaches target tissue (BBB penetration)?

Sufficient receptor binding?

Neuroprotective effect?

If lesion volume affected, then these are right

Dosing regimen

Plasma levels

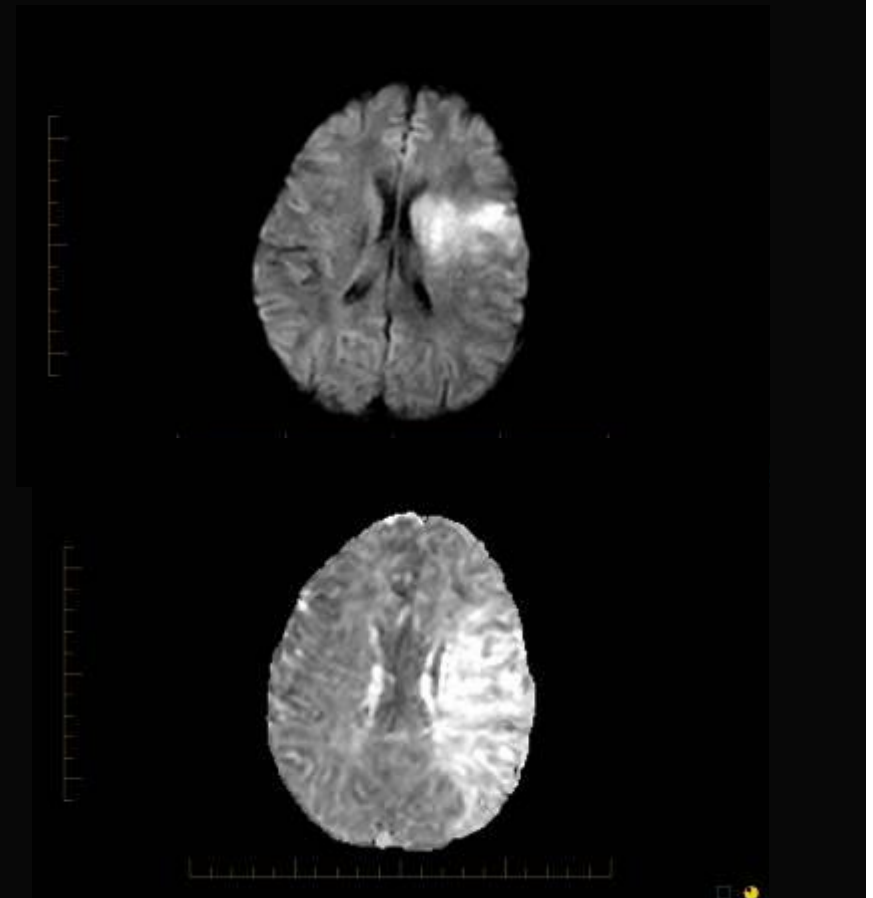
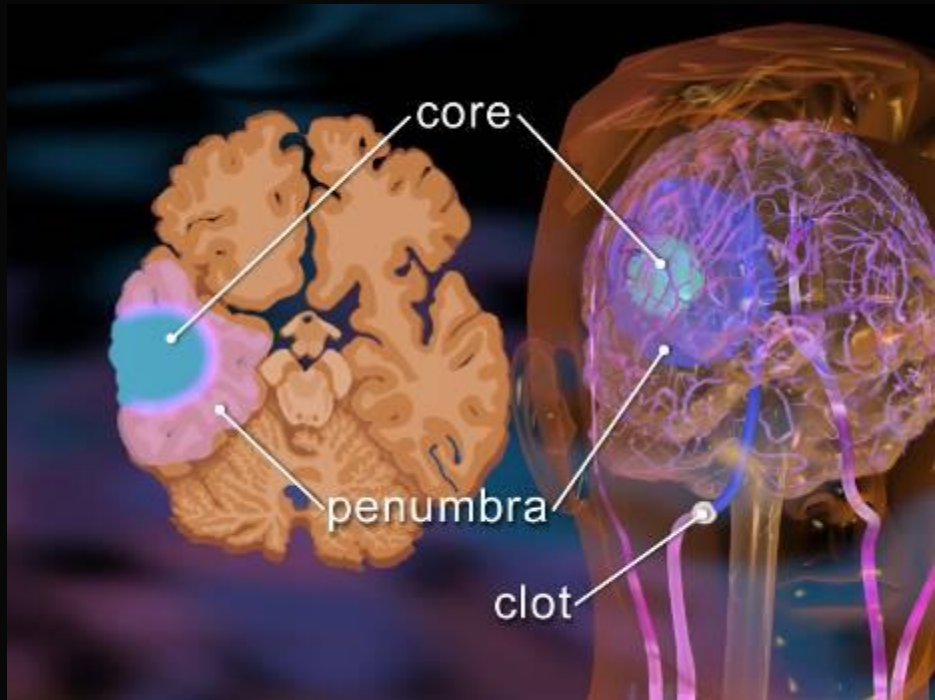
Drug reaches target tissue (BBB penetration)

Sufficient receptor binding

Neuroprotective effect

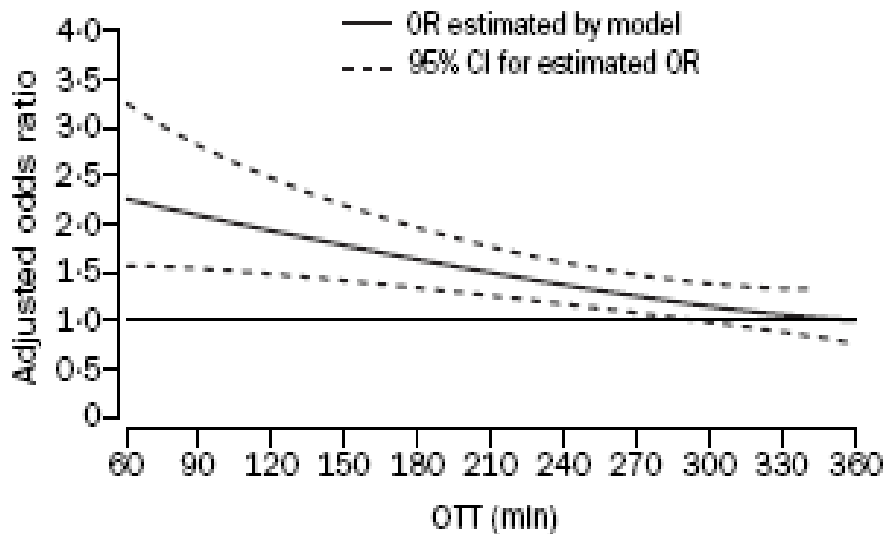
Diffusion-Perfusion Mismatch approximates ischemic penumbra

Optimal target population for stroke trials



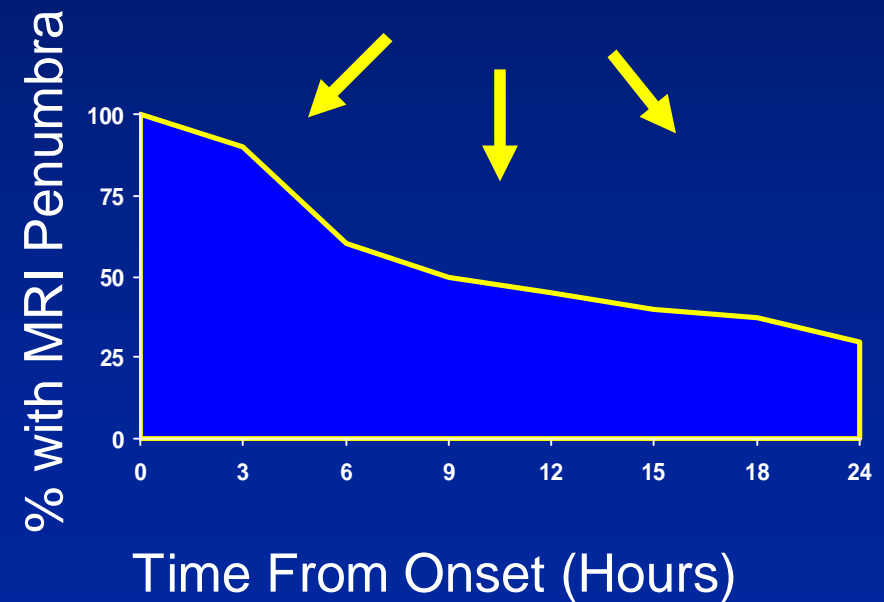
As time proceeds, patient-specific pathology explains more of the variance in response to therapy

rt-PA efficacy vs. placebo declines with time from onset



rt-PA trialists, Lancet, 2004

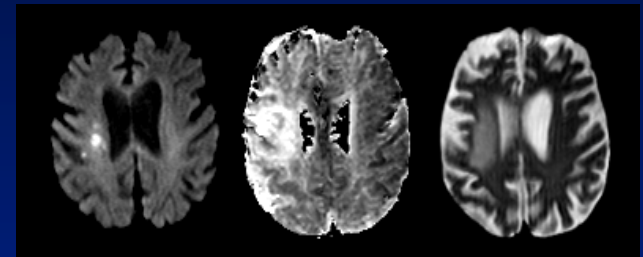
% patients with penumbra declines with time from onset



After Darby et al., Stroke 1999

Imaging in Stroke Clinical Trials

Penumbral Selection
Diffusion-Perfusion Mismatch



Lesion Volume growth is the natural history (~1-2 fold)
Volume change is the outcome measure

Lesion Volume change predicts clinical change

Lesion volume change tracks clinical change

<u>Clinical change</u>	<u>Mean volume change (SEM)</u>
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Clinical response (≥ 7 point NIHSS decrease)	-1.9 (1.8) cc*
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No clinical response	20.0 (5.0) cc
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*p < 0.001

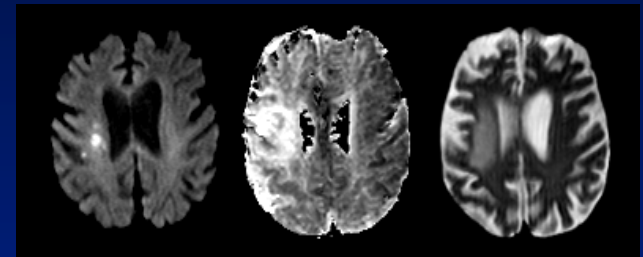
Lesion volume decreases predict clinical improvement

<i>TRIAL</i>	<i>N</i>	<i>PPV</i>
IPI 010	81	0.66
IPI018	131	0.76
POST	111	0.87

Imaging in Stroke Clinical Trials

Penumbral Selection

Diffusion-Perfusion Mismatch



Lesion Volume growth is the natural history (~1-2 fold)

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Lesion Volume change tracks clinical change

Lesion Volume response to Rx predicts clinical response to Rx?

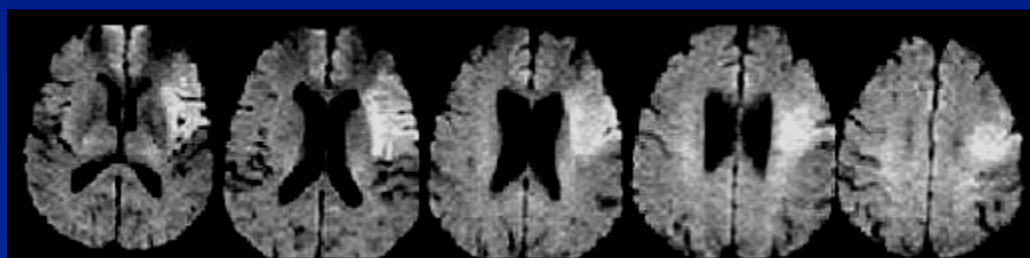
**Does infarct volume predict
good outcome with a proven
therapy?**

Acute to chronic lesion regression predicts clinical outcome with tPA

Clinical Outcome

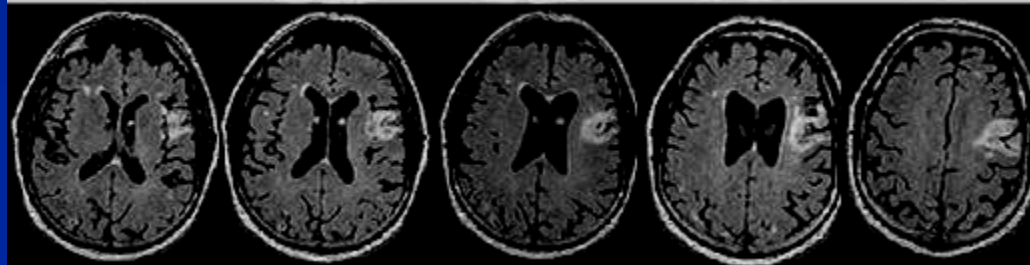
volume decr > 30%	mRS 0-1 (n=29)	mRS 2-6 (n=27)	p
Yes	21	7	.0005 OR = 7.5
No	8	20	

pre-
treatment



DWI
54.1 cc

chronic
(3 month)

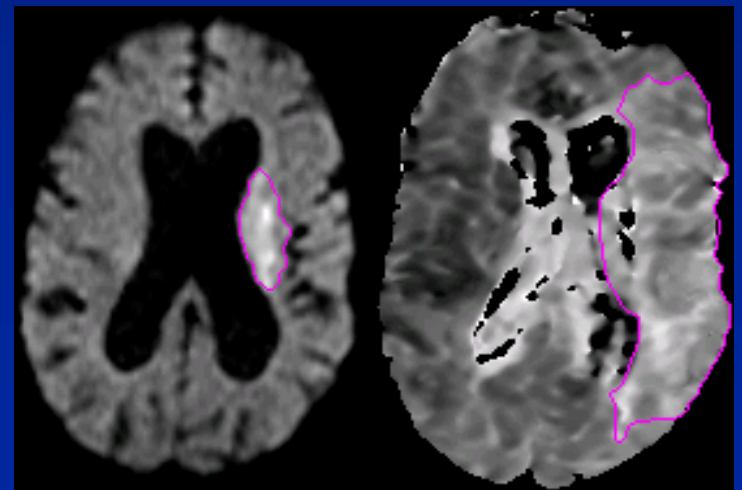


FLAIR
23.5 cc

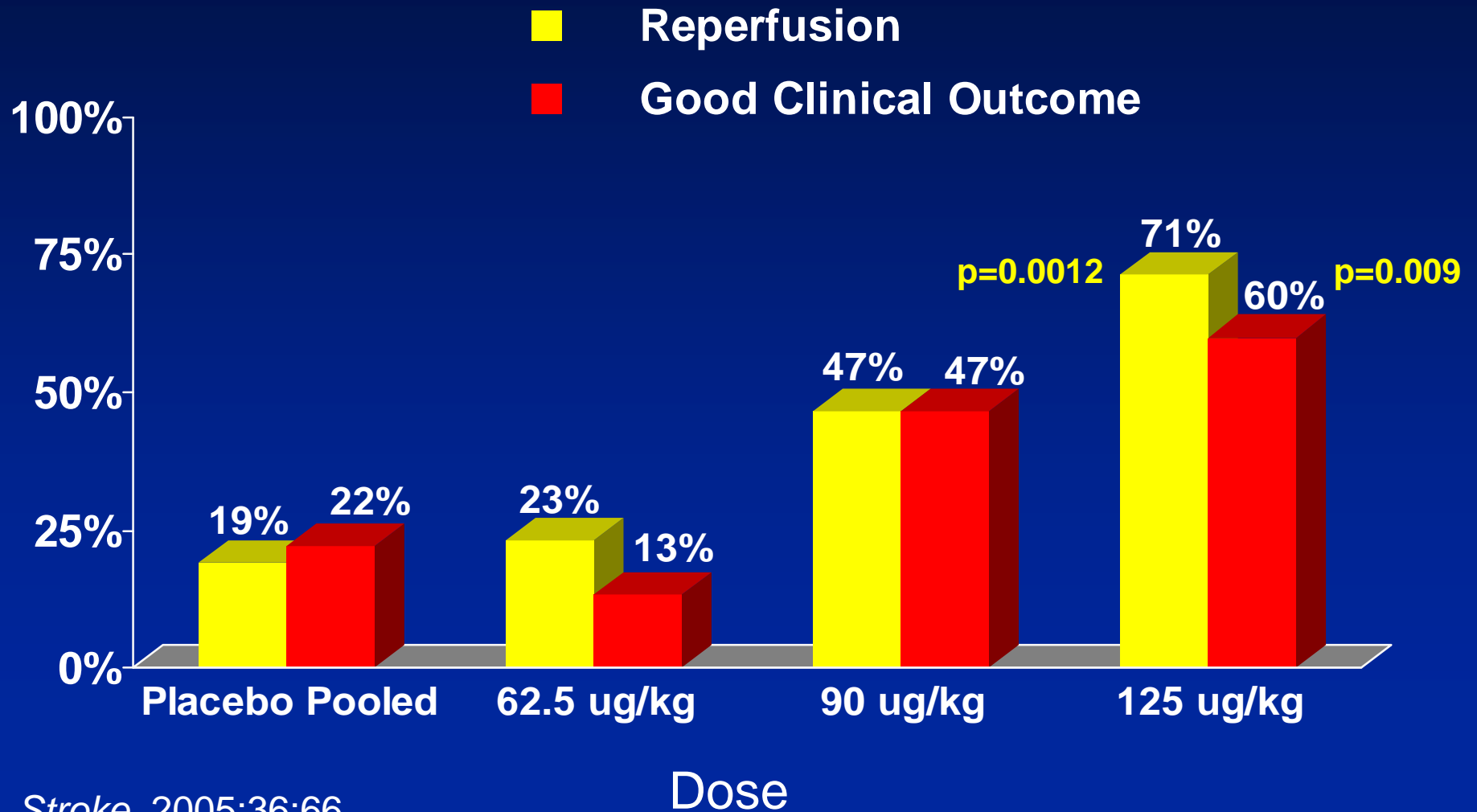
Dose escalation

Example: Desmoteplase in Acute Ischemic Stroke (DIAS)

- n Double-blind RCT
- n Intravenous desmoteplase
 - u N=15 per dose escalation group
- n 3-9 Hrs from onset
- n MRI penumbral pattern
- n Outcome
 - u Early reperfusion
 - u 3 mo clinical



DIAS Reperfusion and Clinical Outcome by Dose



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Summary recommendation

- Poised for high impact
 - ~ 20 MRI acute stroke trials with data available
 - Several international collaborations
 - Strong academic and industrial interest