

# UPDATE ON TREATING ACUTE ISCHEMIC STROKE

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# Presenter Disclosure Information

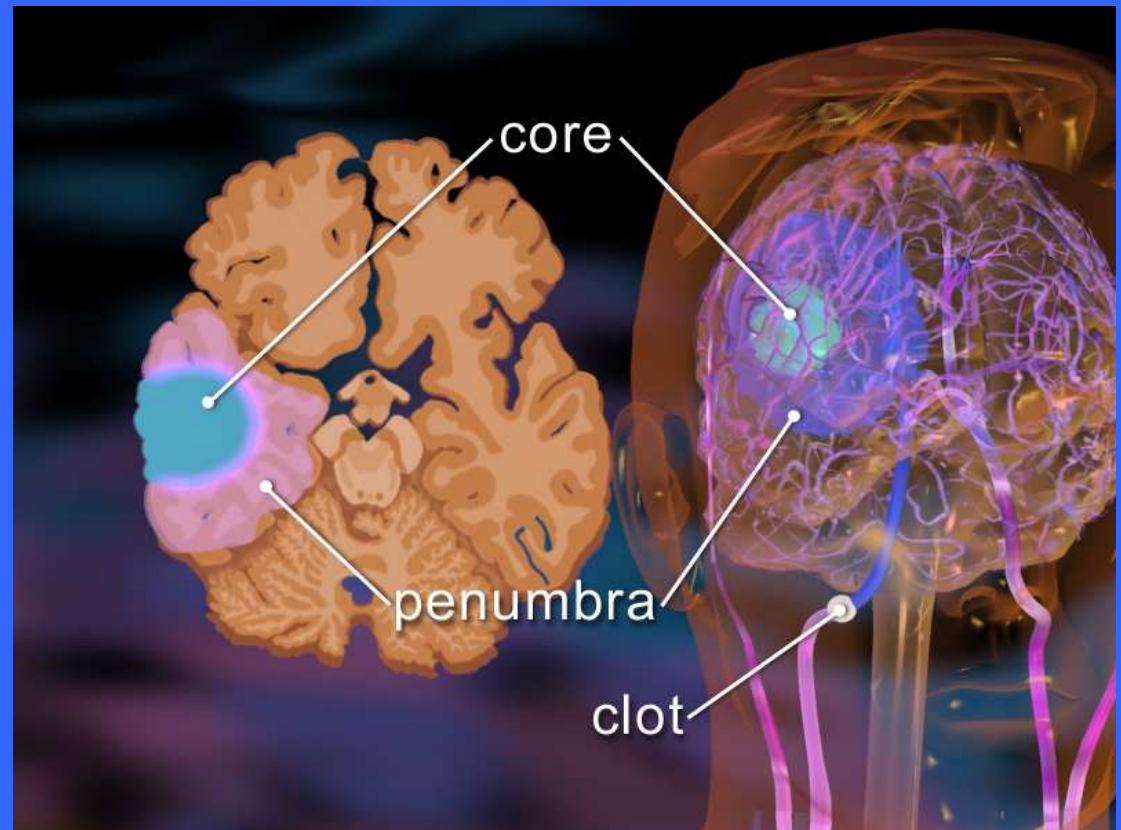
## FINANCIAL DISCLOSURE

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Unlabeled/Unapproved use disclosure: None

# Target of Acute Stroke Therapy in the Ischaemic Penumbra

- Penumbra
  - Brain tissue at high risk of cell death
  - Therapeutic target for agents that improve neuronal tolerance to ischemia



# CONCEPTS OF CELL DEATH IN FOCAL BRAIN ISCHEMIA

- Multiple mechanisms contribute to cell death: protein synthesis dependent and non-dependent
- Their relative contributions relate to the degree of CBF decline, time from onset, metabolic environment and reperfusion
- Different mechanisms likely take precedence simultaneously

# PROGRESSION TO IRREVERSIBLE INJURY

- MULTIPLE MECHANISMS ARE INVOLVED
- ONE TYPE OF INTERVENTION IS LIKELY TO BE OF LIMITED VALUE
- THE RATES OF PROGRESSION VARY AMONG INDIVIDUAL PATIENTS
- THE TARGET OF THERAPY IS ISCHEMIC TISSUE NOT ALREADY IRREVERSIBLY INJURED

# Stroke Therapy Options

- Two primary therapeutic approaches to acute therapy exist
  - Thrombolytic therapy
    - t-PA approved in the US in 1996 for use within 3 hours or less
    - 11%–13% absolute increase in the chance to survive a stroke with minimal or no disability at 3 months
    - < %5 of patients receive i.v. t-PA within 3 hours
  - Neuroprotection
    - No neuroprotective agent is approved today but recent SAINT I results are intriguing

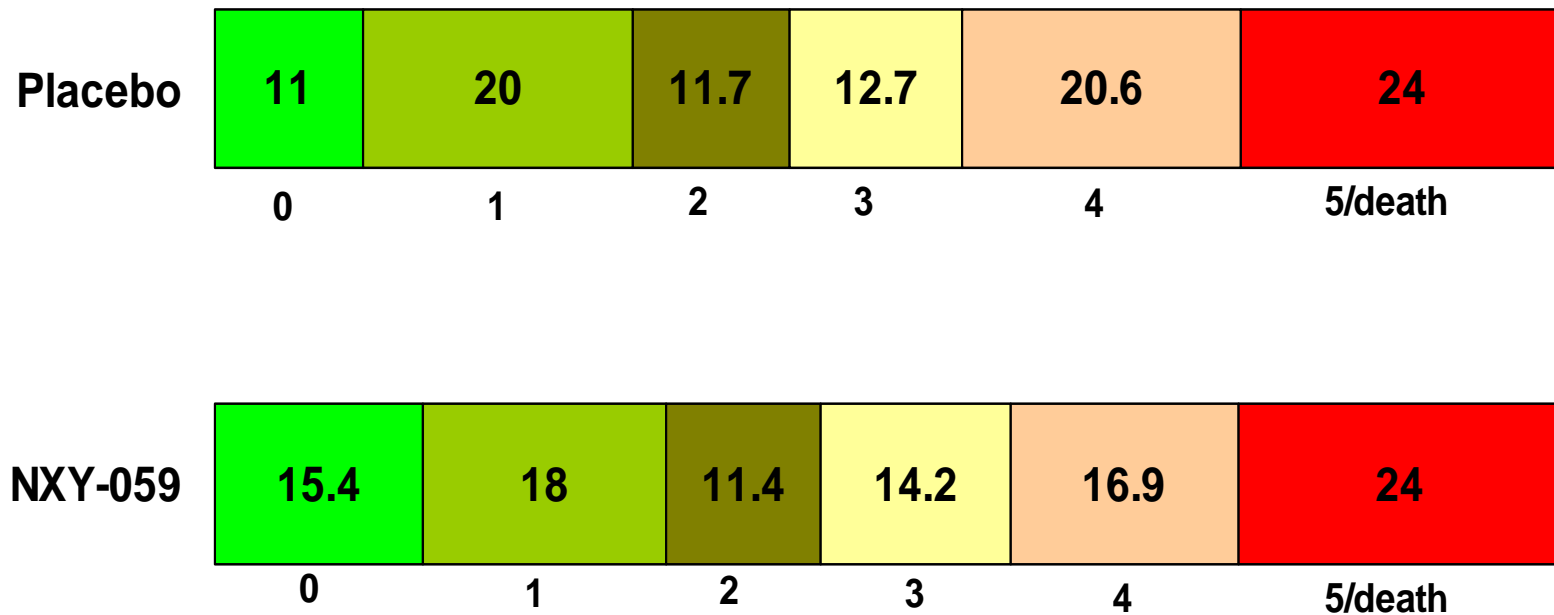
# SAINT I Trial

## Stroke Acute Ischemic NXY-059 Treatment

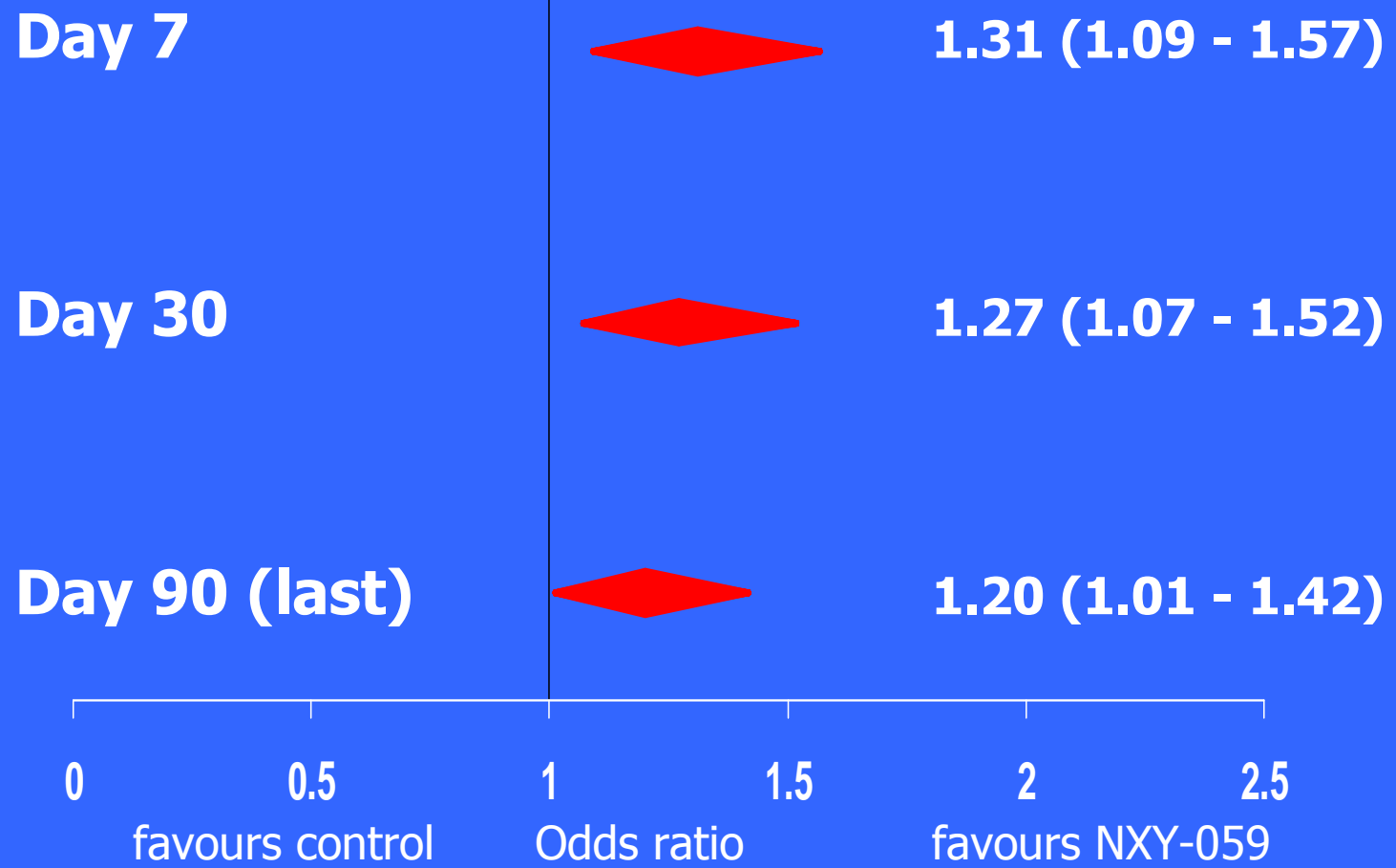
- RCT design
  - 158 centres across 24 countries from Europe, Asia, Australia, South Africa
  - 72-h treatment NXY-059 vs. placebo
  - target plasma concentration of  $\geq 260 \mu\text{M}$ 
    - Range of 150-400  $\mu\text{M}$
- Eligibility
  - Consent, CT/MR-consistent with ischemic stroke, previous independence, conscious, NIHSS  $\geq 6$  including limb weakness,  $< 6$  h from onset to start of treatment, rt-PA permitted
  - forced allocation to achieve mean time from onset to start of treatment  $\leq 4$  h

# Primary outcome (ITT): mRS

$P = 0.038$ , favors NXY-059



# mRS score at Days 7, 30 and 90 (last rating)



# Subgroup Interactions with Primary Endpoint

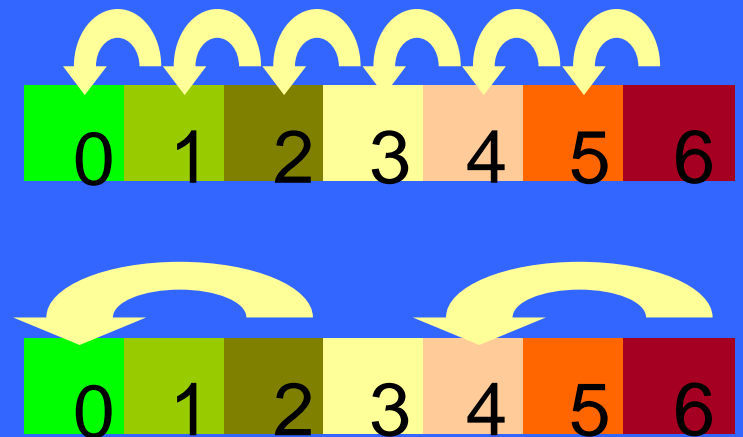
- Treatment-time  $p=0.92$
- Treatment-alteplase  $p=0.93$
- Treatment-severity  $p=0.72$
- Treatment-age  $p=0.62$
- Treatment-diabetes  $p=0.98$
- Treatment-glucose  $p=0.27$

# SAINT I Endpoints

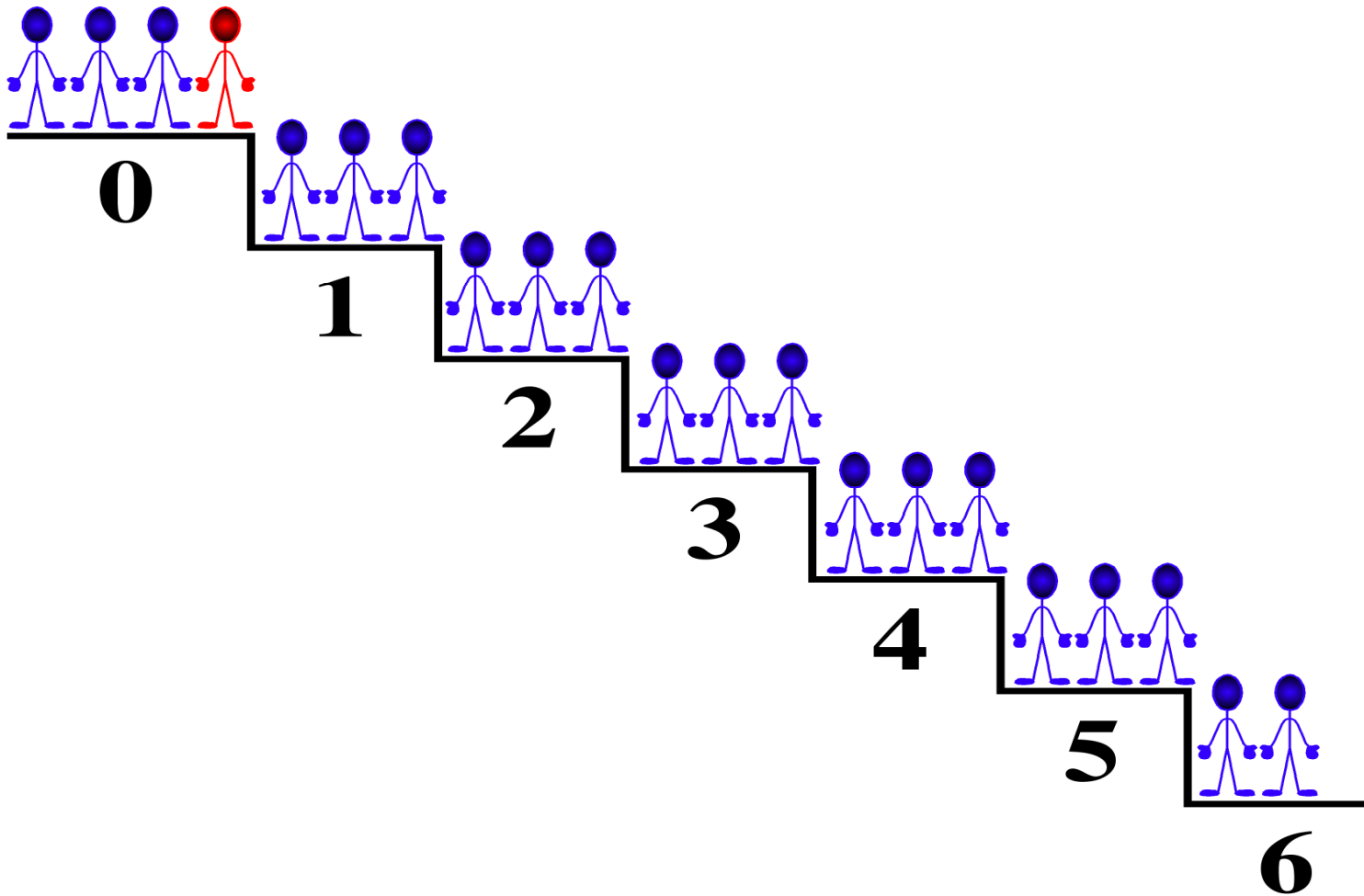
Rankin shift	0.038
Rankin dichotomized 0-1 v 2-6	0.17
Improvement in NIHSS	0.86
Barthel index dichotomized	0.14
Stroke Impact Scale	0.08
EuroQOL Index	0.06
QOL Visual Analogue Scale	0.05

# Shift Analysis

- Improvement anywhere along outcome scale
  - “Does the treatment make the patient better *to some degree*?”
- Advantages
  - Analyzes achievable goals for each patient
  - Polychotomous
    - Incorporates benefits at all state transitions
    - Incorporates harmful effects occurring at all state transitions
  - Does not require knowledge of likely treatment impact
  - Increases signal
- Disadvantages
  - Computationally complex
  - Increases noise\*
  - Difficult to express treatment effect in clinical/lay terms

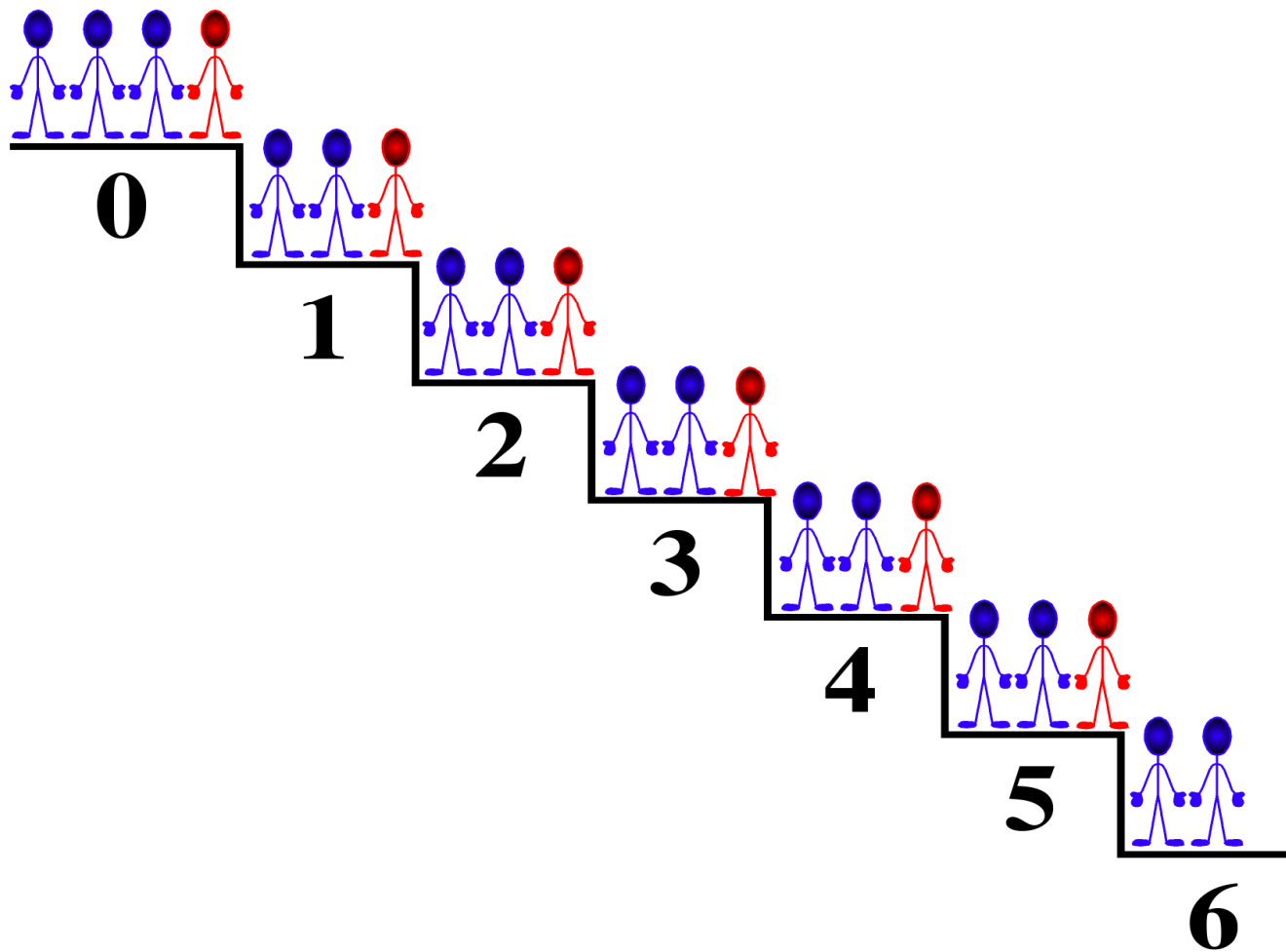


\*E.g. Improvement in NIHSS



1 of 21  
benefit

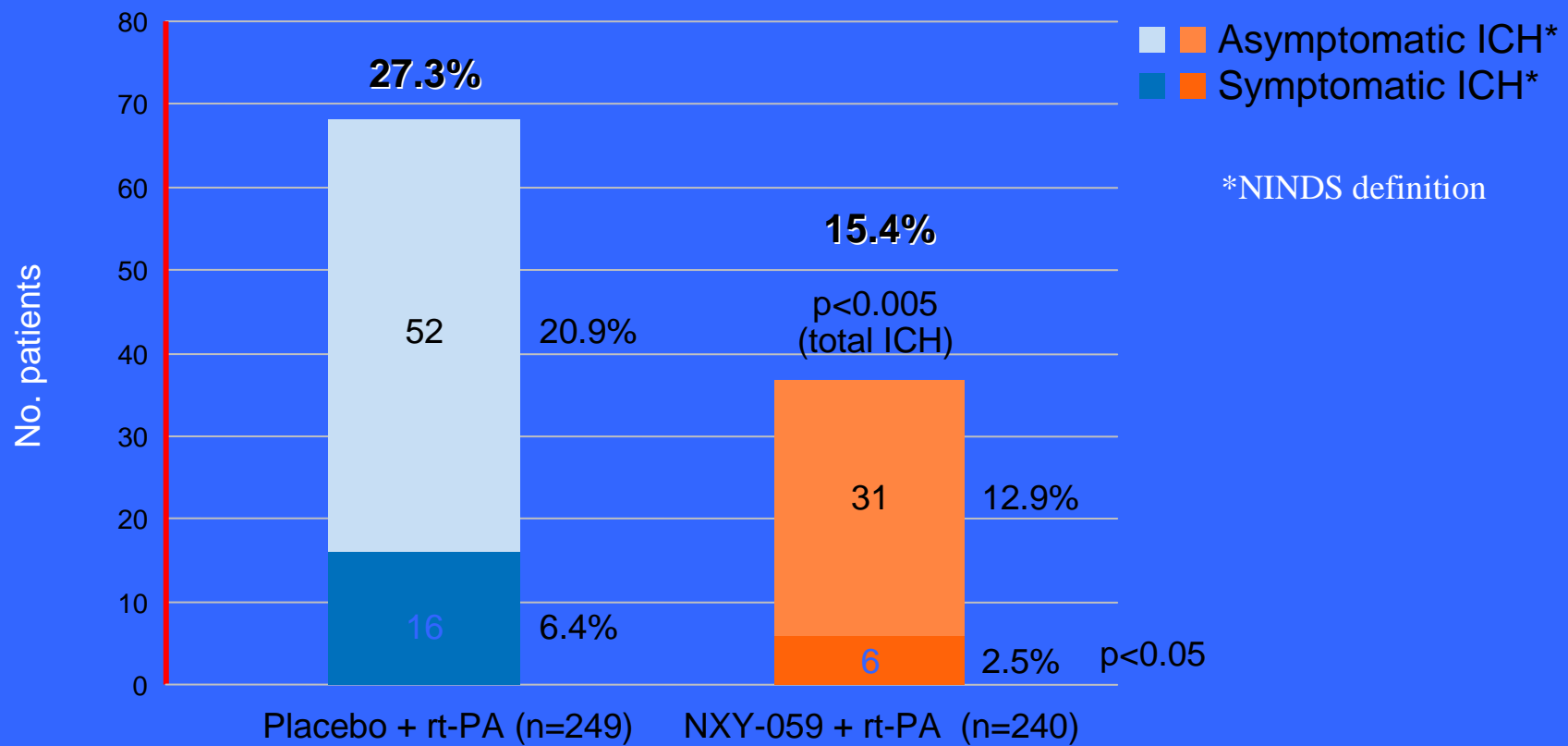
NNT =  
21



6 of 21  
benefit

$$\text{NNT} = 3.5$$

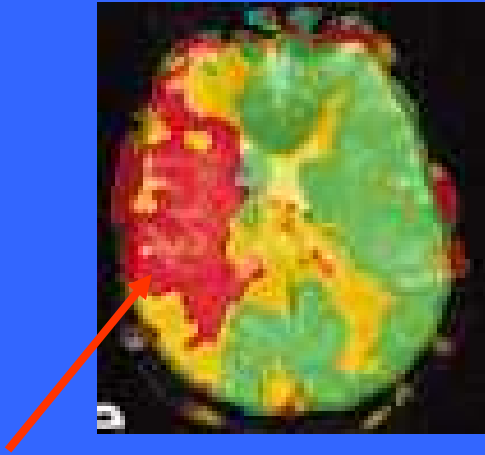
# ICH After Thrombolysis



# Clinical Impact of NXY-059

- NNT is approximately 10
- For every 100 patients treated with NXY-059, 10 improve by one or more clinically important steps on the modified Rankin Scale
- No definite evidence of harm
- Most physicians/patients would judge the therapy as worthwhile because improving from 4-3, 3-2 or 2-1 on the mRS is clinically meaningful
- Confirmatory trial required and enrollment for SAINT-II is complete

# The MISMATCH HYPOTHESIS



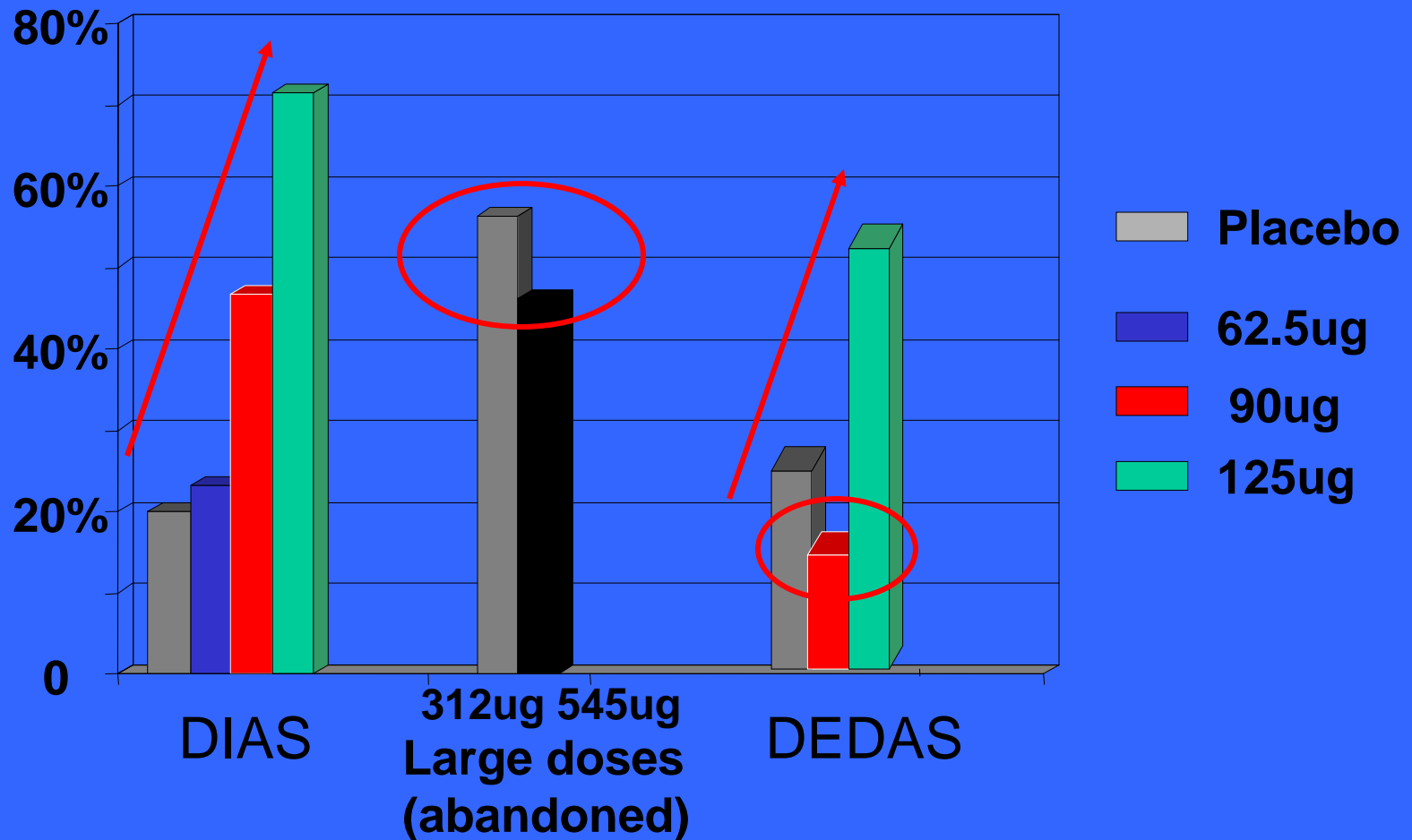
PWI = ischemia

DWI = core within ischemia

PWI – DWI = salvagable ischemic tissue  
(« approximates the penumbra »)

# DIAS/DEDAS: 3-9 hours, mismatch patients

N=141. Reperfusion rates



→ Right direction

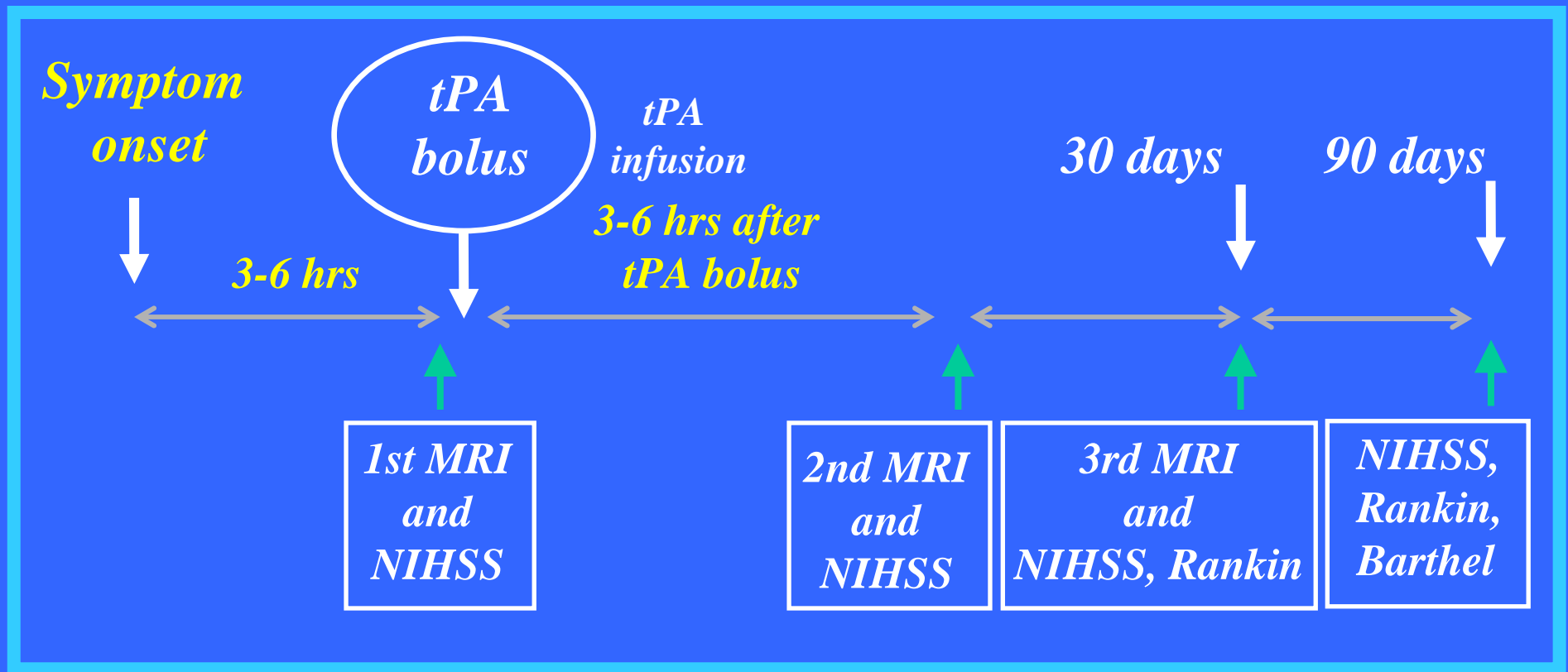
→ Small numbers of patients give less solid results

# The DIAS/DEDAS - evidence

- The trials were well designed and well performed
- The results are promising and deserve further testing in phase III trials

... and the MRI-mismatch selection criterion needs to be reduplicated with other recanalisation strategies, in other studies, and with other time frames before it is ready for prime time.

# DEFUSE Study



# Results

## Feasibility (baseline)

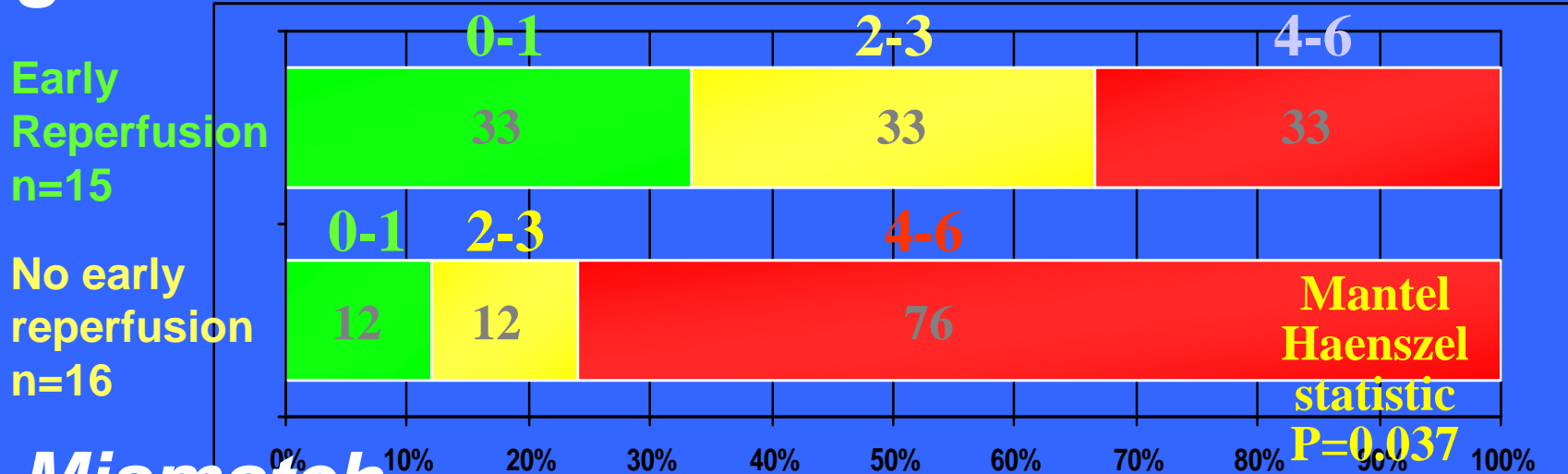
- DWI: 100% success
- PWI: 92% success
- MRA: 92% success

## MRI Results

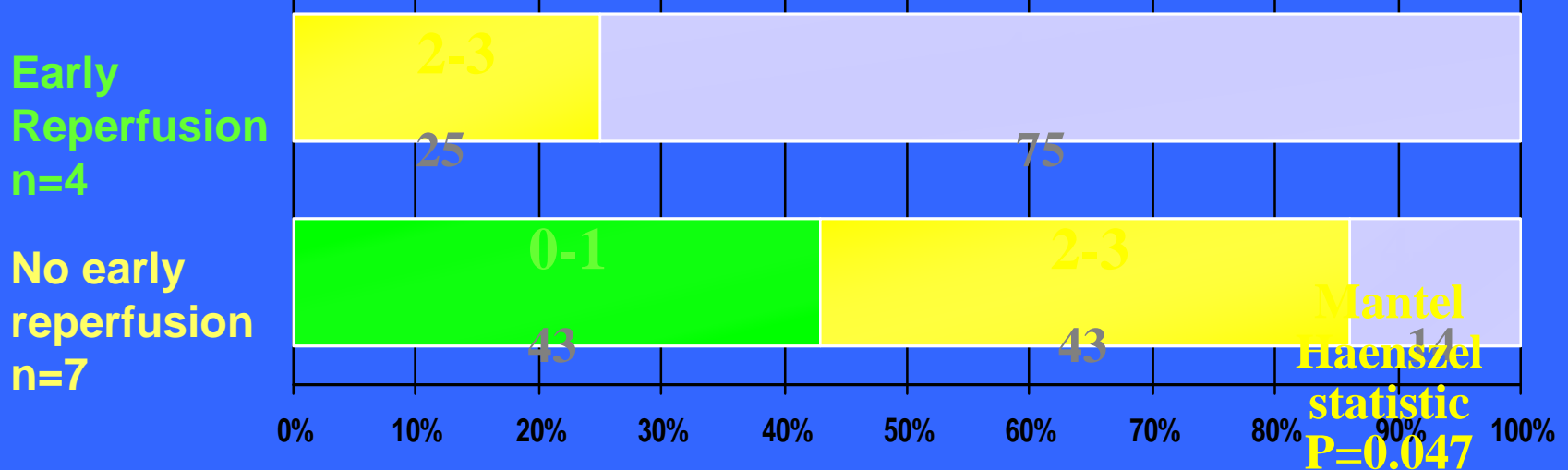
- Mismatch (PWI 1.2X > DWI) in 54%
- MRA abnormality in 68%
- Early reperfusion in 49%
- Early recanalization in 43%

# DAY 30 mRS

## Target Mismatch



## No Mismatch



# OPEN STUDIES OF I.V. TPA 3-6 HOURS WITH DWI/PWI-RIBO

- 122 patients treated, 79 0-3 hrs, 43 3-6 hrs
  - All of 3-6 hr patients had >50% mismatch
  - Baseline severity similar in the 2 groups
  - 2-hour recanalization rates, 49 and 55%
  - 3 month mRS 0-2, 42% and 38%
- 
- Stroke 2005;597-602

# Thomalla et al. German Multicenter Study

- 174 patients, 108 0-3 hrs, 66 3-6 hrs
- 85% had >20% mismatch
- Baseline characteristics similar in the 2 groups
- 3 month mRS 0-2, 64% 0-3 hr group and 53% 3-6 hr group
  
- Stroke 2006;852-858