Breaking news from IST-3

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on behalf of the IST-3 collaborative group

ESC London

29th May 2013

MRC Medical Research Council

IST-3 Thrombolysis

Disclaimer & disclosures

- I will present relevant data from current research and there may be data or statements not covered by current regulatory approval. This presentation does not suggest clinical use beyond regulatory approval.
- Please always check the most current prescribing information as approved for your country.
- IST-3 was conducted completely independently. BI donated drug and placebo for the first 300 patients in IST-3 **and thereafter made no financial contribution, & had no role in data collection, analysis, reporting or the decision to publish**.
- IST-3 disclosures in full in Lancet publication

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Outline

- IST-3 main features
- Predicting early risk (SICH < 7 days) and benefit at 6 months.
- Longer-term outcomes;18 months (*in press, Lancet Neurology)*
  - Survival
  - Functional status (OHS) & quality of life
  - Living at home, institution
- What's still to come?

Main features of IST - 3

- Prospective, randomised, open, controlled study of i.v. rt-PA vs control,
- 3035 acute ischaemic stroke < 6 hours, 95% did not meet terms of EU approval, 54% aged > 80yrs
- **Primary outcome at 6 months**: Oxford Handicap Scale (OHS) : % 'alive and independent' (OHS 0-2)
- **Secondary outcomes at 18 months**: death, OHS, HRQoL, Living circumstances

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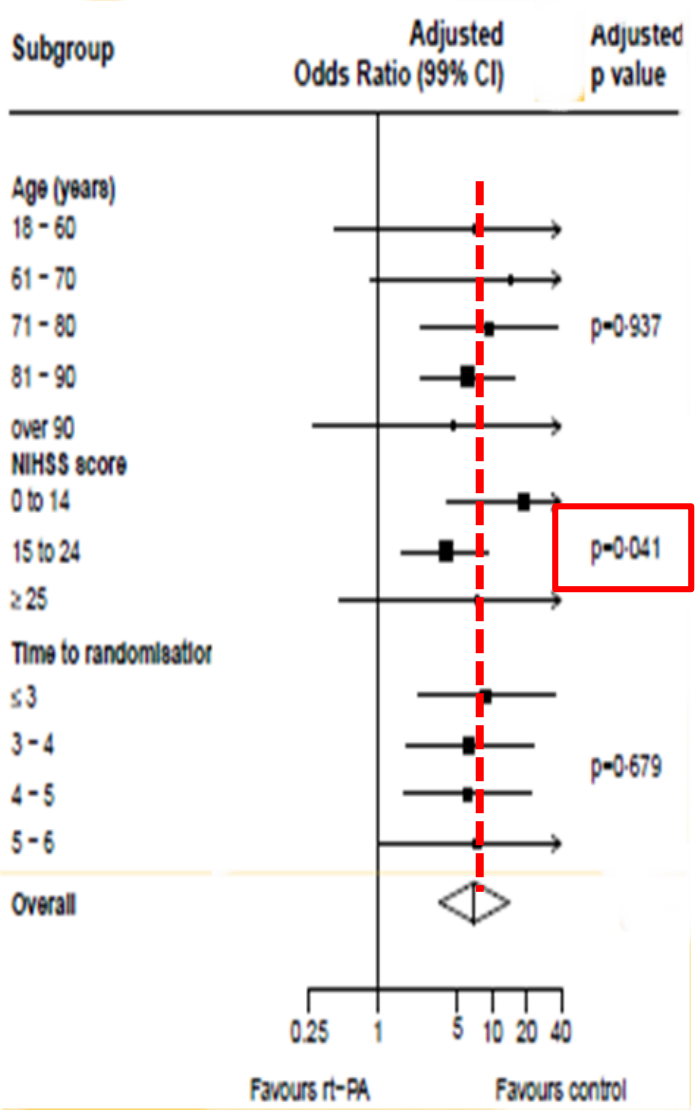
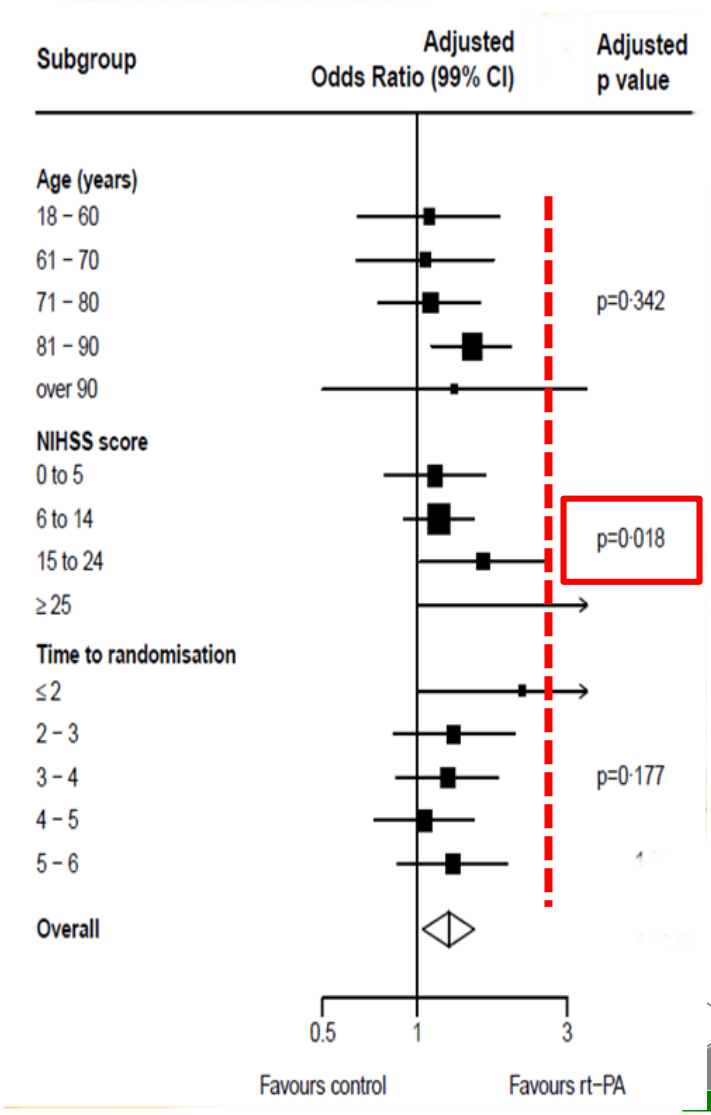
Risks, benefit and interactions in IST-3. For each subgroup consider:

- early RISK = excess risk of symptomatic ICH < 7 days
- net BENEFIT = at 6 months, shift in OHS grade in an ordinal analysis

SICH < 7d



Ordinal OHS at 6 mo.



Need a larger dataset…

= individual patient data meta-analysis of all the i.v. rt-PA trials

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International Journal of Stroke
Early View, Article first published online: 3 MAY 2013
Abstract | Full Article (HTML) | References | Cited By
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Randomised controlled trial data for iv rt-PA on 6756 patients,

Protocols

Details of a prospective protocol for a collaborative meta-analysis of individual participant data from all randomized trials of intravenous rt-PA vs. control: statistical analysis plan for the Stroke Thrombolysis Trialists' Collaborative meta-analysis

The Stroke Thrombolysis Trialists' Collaborative Group[1]*

Rationale Thrombolysis with intravenous alteplase is both effective and safe when administered to particular types of patient within 4·5 hours of having an ischemic stroke. However, the extent to which effects might vary in different types of patient is uncertain.

Aims and Design We describe the protocol for an updated individual patient data meta-analysis of trials of intravenous alteplase, including results from the recently reported third International Stroke Trial, in which a wide range of patients enrolled up to six-hours after stroke onset were randomized to alteplase vs. control.

the extent to which the known benefit of alteplase on modified Rankin Score 0–1 diminishes with treatment delay, and the extent to which it is independently modified by age and stroke severity. Key secondary outcomes include effect of alteplase on death within 90 days; analyses of modified Rankin Score using ordinal, rather than dichotomous, methods; and effects of alteplase on symptomatic intracranial hemorrhage, fatal intracranial hemorrhage, symptomatic ischemic brain edema and early edema, effacement and/or midline shift.

Discussion This collaborative meta-analysis of individual par-

Data exchange between BI and IST3

STTC analysis plan

Primary analyses:

- After what treatment delay is benefit lost or does harm begin?
- Do age or stroke severity modify the proportional effect of rt-PA on stroke outcome?

Secondary analyses

- Effect of treatment allocation on: death within 90 days, SICH?
- Effect modification by other baseline characteristics?

Long-term outcome

Lancet Neurology 2013

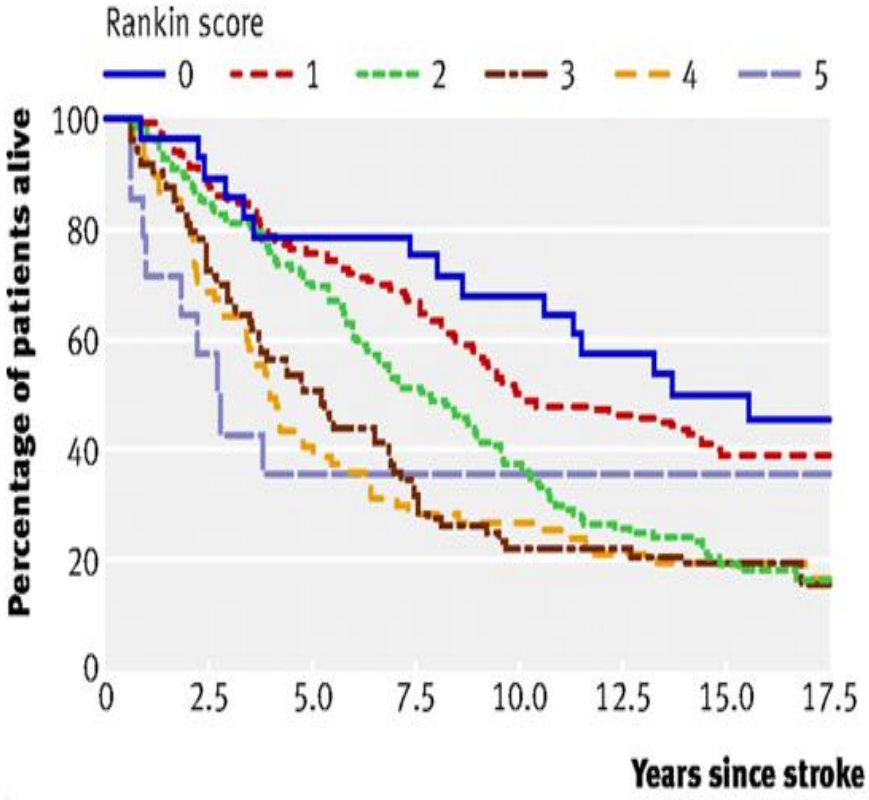
(in Press)

Performing Cost-Effectiveness Analysis by Integrating Randomized Trial Data with a Comprehensive Decision Model: Application to Treatment of Acute Ischemic Stroke

Gregory P. Samsa,[1–3,] Richard A. Reutter,[4] Giovanni Parmigiani,[1,4,6]*

ABSTRACT. A recent national panel on cost-effectiveness in health and medicine has recommended that cost-effectiveness analysis (CEA) of randomized controlled trials (RCTs) should reflect the effect of treatments on long-term outcomes. Because the follow-up period of RCTs tends to be relatively short, long-term implications of treatments must be assessed using other sources. We used a comprehensive simulation model of the natural history of stroke to estimate long-term outcomes after a hypothetical RCT of an acute stroke treatment. The RCT generates estimates of short-term quality-adjusted survival and cost and also the pattern of disability at the conclusion of follow-up. The simulation model incorporates the effect of disability on long-term outcomes, thus supporting a comprehensive CEA. Treatments that produce relatively modest improvements in the pattern of outcomes after ischemic stroke are likely to be cost-effective. This conclusion was robust to modifying the assumptions underlying the analysis. More effective treatments in the acute phase immediately following stroke would generate significant public health benefits, even if these treatments have a high price and result in relatively small reductions in disability. Simulation-based modeling can provide the critical link between a treatment's short-term effects and its long-term implications and can thus support comprehensive CEA. J CLIN EPIDEMIOL 52;3:259–271, 1999.

Epidemiology: level of function at six months (mRS or dependency) after stroke predicts long-term survival



OCSP

IST-1 UK

Slot K B et al. BMJ 2008;336:376-379

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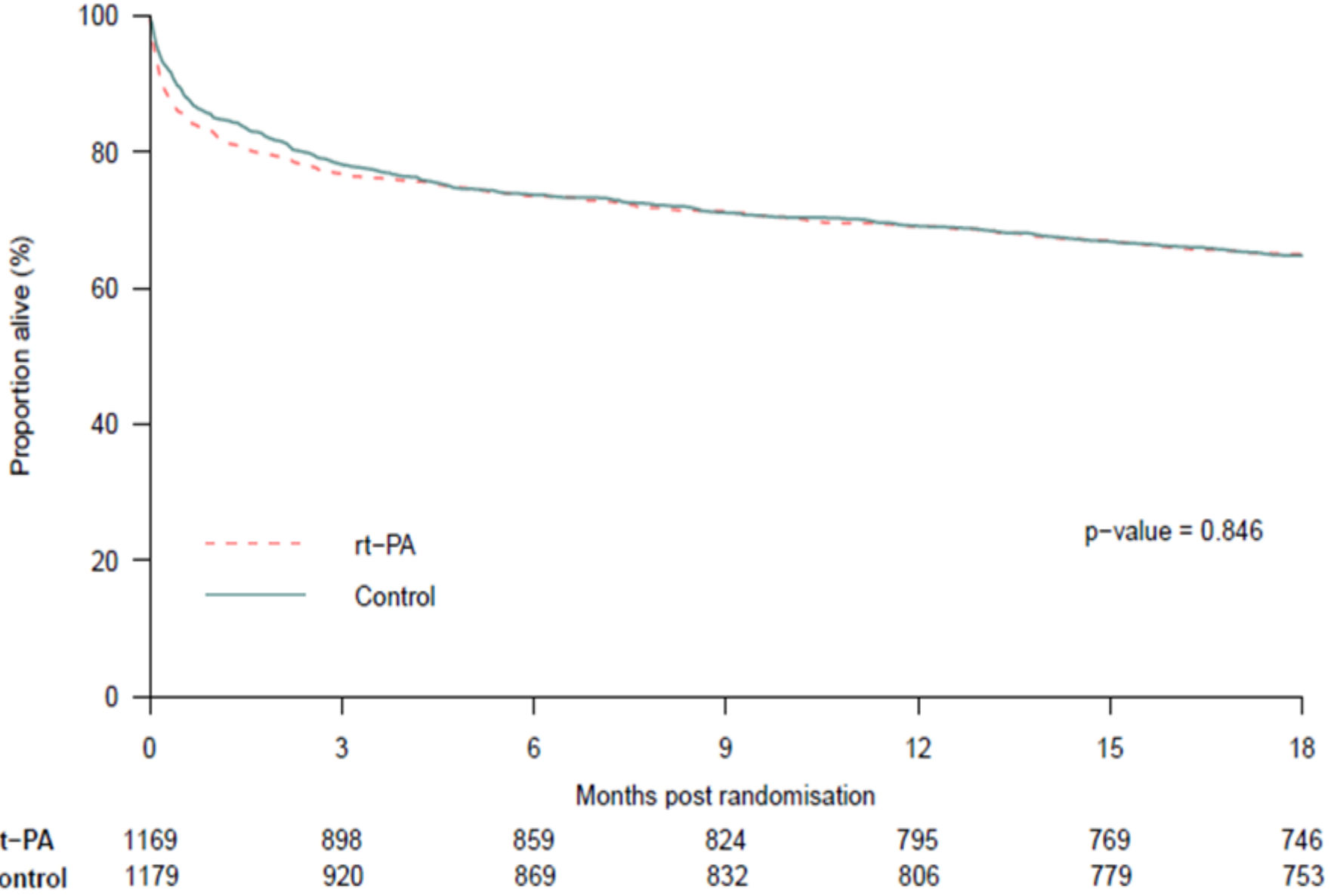
IST-3: survival to 18 months



rt−PA	1169	898	859	824	795	769	746
Control	1179	920	869	832	806	779	753

At 18 months, % 'alive & independent' (OHS 0-2)

rt-PA (n=1169)*		control (n=1179)*	
n	(%)	n	(%)
391	(35%)	352	(31%)

Adjusted odds ratio 1.28
(95% CI 1.03 -1.57) p = 0.024
= 36/1000 more alive and independent

*N= 2248 patients in 18-month follow-up cohort

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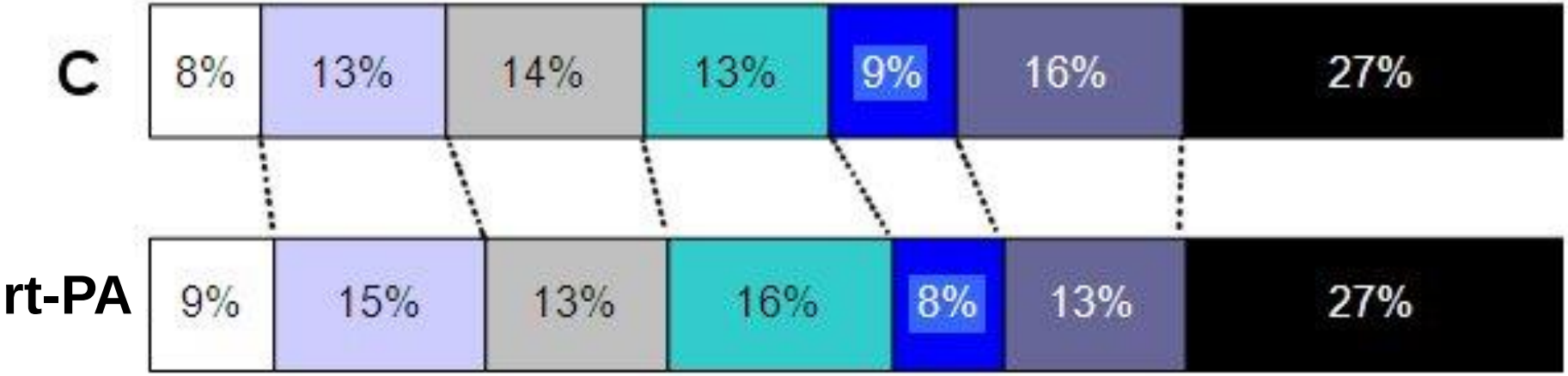
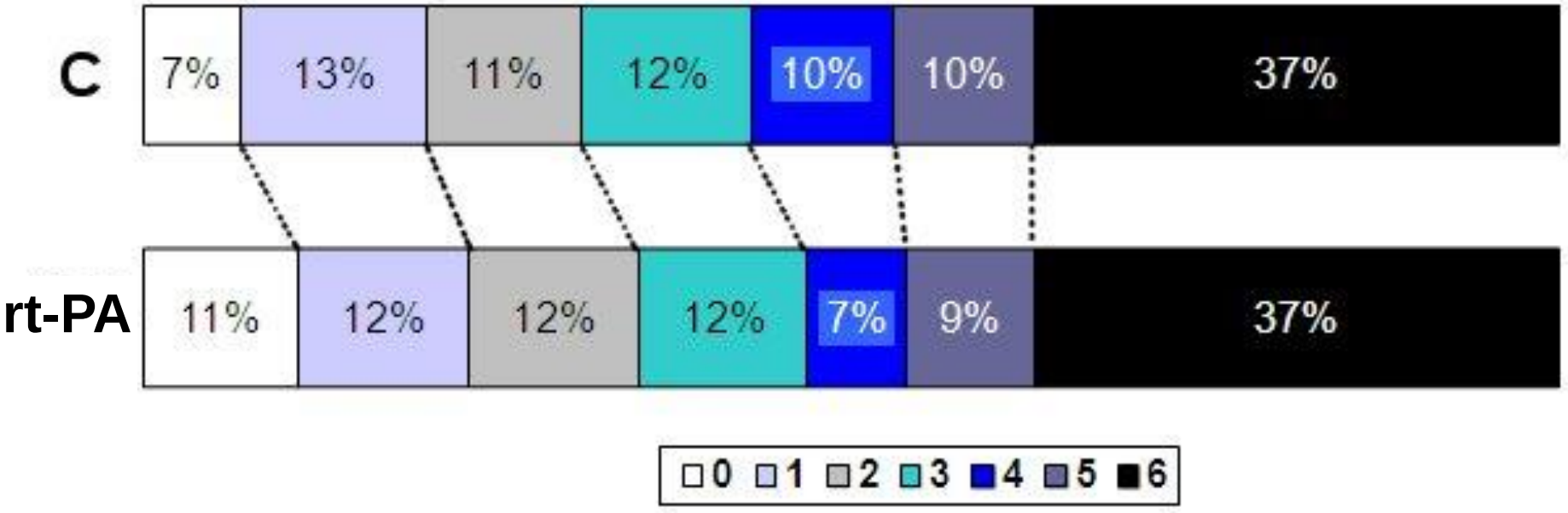
Ordinal 6 months p=0.001



Ordinal 18 months p=0.002



At 18 months, % of survivors living at home

rt-PA (n=709)		control (n=707)	
n	(%)	n	(%)
574	(81%)	553	(78%)

Adjusted odds ratio OR=1·32, (95% CI 1·00 to 1·73) p = 0·05

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IST-3: still to come

Imaging: ***Auditorium Thursday 12:20***.

Wardlaw. IST-3: Does perfusion imaging lesion size or mismatch influence six month outcomes after rt-PA given up to six hours after acute ischaemic stroke?

Risk and benefit: ***Room 17 Thursday 17:00***. Whiteley. IST-3: Predictions of intracranial haemorrhage and the risks and benefits of rt-PA in acute ischaemic stroke

Health economic analysis

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Take home messages

- Pre-treatment antiplatelet & higher NIHSS -> higher SICH risk, but **benefit NOT reduced**
- Risk of SICH with rt-PA is **NOT** time-dependent, but benefit **IS**
- STTC will provide reliable evidence on factors modifying SICH risk & response to treatment
- Long-term outcome is important: benefits of thrombolysis are still evident at 18 months
- Even modest gains in function may translate to long-term survival benefit – longer FU ongoing

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Acknowledgements:

The 3035 patients, 156 hospitals in the IST-3 group, 12 National Coordinators, Data Monitoring Committee, MRC Steering Committee, Image Reading Panel, Event adjudication panel,.

Stroke association

MRC Medical Research Council

The Health Foundation

afa

The Research Council of Norway

Australian Government National Health and Medical Research Council NHMRC

Heart Foundation

Chest Heart & Stroke Scotland

Hjärt Lungfonden

Regione Umbria

DALHOUSIE UNIVERSITY Inspiring Minds

Schweizerische Herzstiftung
Fondation Suisse de Cardiologie
Fondazione Svizzera di Cardiologia

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