

# THE IST-3 TIMES

October 2008



## RECRUITMENT AT 1<sup>st</sup> October 2008

UK	512
Poland	193
Norway	147
Sweden	132
Italy	116
Australia	102
Belgium	59
Austria	17
Canada	7
Mexico	3
<b>Total</b>	<b>1288</b>

## TOTAL NUMBER OF PATIENTS RECRUITED TO DATE:

# 1288

## NUMBER OF CENTRES PER COUNTRY

UK:	35
Italy:	19
Sweden:	14
Norway:	12
Australia:	10
Poland:	5
Belgium:	3
Austria:	2
Portugal:	2
Canada:	1
India :	1
Mexico:	1
Switzerland:	1

**Total** **106**

## EDITORIAL

Professor Peter Sandercock, Co-Chief Investigator



### ECASS-3 Results Published. IST-3 DMC Recommends IST-3 to Continue Recruitment

#### Summary of ECASS-3 results

The ECASS-3 trial reported its results at the World Stroke Conference in Vienna and at the same time in the New England Journal of Medicine at the end of September (*Hacke W, et al. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. The NEJM 2008;359:1317-29*). Patients aged < 80 were eligible for ECASS-3 if: they had an acute ischaemic stroke; could be treated within 3 & 4.5 hours of onset: and, met the strict criteria of the EU approval (these are listed in detail in the paper). It enrolled a total of 821 patients, and the median time for the administration of alteplase was 3 hours 59 minutes, Median NIHSS was 9 in the alteplase group and 10 in placebo. Defining favourable outcome as mRS score of 0–1, more patients had a favourable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; P = 0.04). Defining favourable outcome as mRS score of 0–2, the odds ratio was similar, 1.30 (95% confidence interval 0.95–1.78), but not significant (p= 0.11). Helpfully, the trial reported the risk of symptomatic intracerebral haemorrhage (SICH) according to a number of different definitions; of these, the definition preferred by the ECASS-3 investigators is also the one that most closely matches the IST-3 definition. The frequency of SICH was low: 2.4% for alteplase vs. 0.2% vs. for placebo (OR 9.85 (95% confidence interval 1.26–77.32), p= 0.008.)

#### Implications of these results for IST-3

These results are clearly excellent news for people with acute stroke and for IST-3, since they reinforce the need to establish services to deliver thrombolysis to appropriate patients aged less than 80 years. This will increase the number of centres able to participate in IST-3, and hence help to answer some of the remaining questions about the use of this treatment. How should we respond to these results? It is helpful first to consider the views of the IST-3 DMC, which reviewed the accumulating data in the trial, the data from ECASS-3 and the update of the Cochrane systematic review of randomised trials of thrombolysis for stroke, prepared by Joanna Wardlaw and Veronica Murray. The DMC opinion is set out on page 2 in the letter from Professor Rory Collins.

## Letter from Professor Rory Collins, chairman of IST-3 Data Monitoring Committee

Dear Peter

### IST-3 DMC meeting 23rd September 2008

In preparation for the release of the ECASS-III results (and blind to those results), the IST-3 Data Monitoring Committee had arranged a teleconference for today (23 September 2008). Our review of the available data from IST-3 and the other trials, including safety information from ECASS-III, does not lead us to consider there to be any need for a change to IST-3. We would encourage the IST-3 collaborators to maintain the increase in the rate of recruitment. The DMC will continue to monitor interim results from IST-3 as planned.

Yours sincerely

Professor Rory Collins  
Chair, IST-3 DMC

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### Implications of these results for use of thrombolysis 'within license'

At a population level, in North America and Europe, between 1% and 3% of all ischaemic strokes are currently treated with thrombolysis (though of course, in some centres, the proportion is much higher). As a result of ECASS-3, the proportion treated should continue to increase, but even an 'extended time' licence will still exclude many from treatment, and the public health benefit will still be limited. We understand a formal extension to the licence may not occur until 2010. Whatever happens with the EU license, we still need IST-3 to determine if a **much** wider range can be treated, and so have a much greater public health impact. The table below assumes 130,000 strokes per year in the UK, and 2% of all ischaemic strokes treated with thrombolysis, which might plausibly extend to 30% if IST-3 is positive.

#### How many stroke patients per year in UK\* might avoid being 'dead or dependent' with each treatment?

	% treated with this intervention	Number treated per year	Benefit per 1000 treated	Number who avoid death or dependency
Aspirin	80%	104000	13	1350
Stroke Unit	60%	78000	56	4370
Thrombolysis <sup>1</sup>	2%	2080	63	130
Thrombolysis <sup>2</sup>	30%	31200	47	1470

1. Current UK rates estimated to be much lower, but this figure would be a feasible target, given the current approval by NICE. 2. Potential outcome if IST3 is positive.

#### Even if the EU approval for thrombolysis is extended to 4.5 hrs, this will still exclude patients who

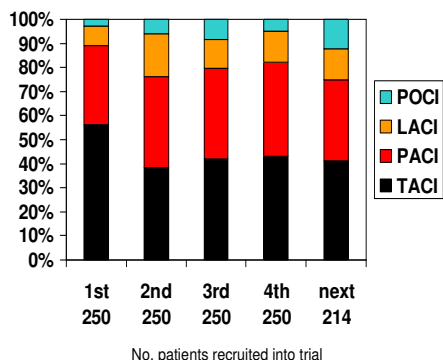
- Are aged > 80 years
- Have either 'very mild stroke' or NIHSS > 25
- Have a history of prior stroke within the last 3 months
- Have a history of prior stroke + Diabetes
- Arrive at hospital too late after onset (4.5 to 6.0 hours)
- Have other relative contraindications specified in the licence (e.g. CT 'extensive infarction')

We have therefore reviewed the characteristics of patients being recruited in the trial.

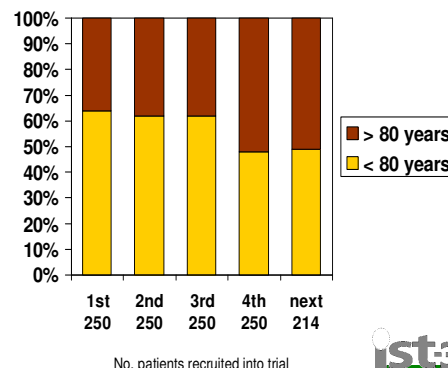
## Characteristics of the 1214 patients recruited in IST-3 by July 2008

The great majority were recruited in the 3-6 hour window (some patients aged over 80 were recruited < 3hrs), with a median time to randomisation of 4.0 h. IST-3 is now the largest randomised controlled trial in 'older' patients with hyper-acute stroke with 838 patients aged > 70 years, and 530 patients > 80 years. The trial includes patients with a wide range of severities; quite a number with NIHSS > 25 and some with NIHSS ≤ 4. The median severity was 11 (higher than ECASS-3). The figure shows the distribution of OCSP subtype and it also shows that we have recruited subtypes not much recruited in previous trials: 153 Lacunar infarcts, 77 Posterior circulation infarcts to date.

Trends in type of patient recruited since trial began: Infarct subtype



Trends in type of patient recruited 2000-2008: AGE



## Discussion at collaborators meeting in Vienna; summary of main points

- ECASS-3 results were positive, but only apply to patients under 80, within 3-4.5 hours of onset who, apart from time from onset, meet the strict terms of the current EU licence
- IST-3 group members at the meeting agreed the ECASS-3 results would stimulate more centres to offer a thrombolysis service, which would be good.
- We would all continue to recruit eligible patients in IST3.
- There was discussion about whether or not to randomise patients aged under 80, presenting 3-4.5 hours; if the patient otherwise met the terms of the current licence, we agreed we would generally treat such patients.
- However, we agreed that it could still be appropriate to randomise selected patients at 3-4.5 hrs, especially if
  - they had one of the relative contraindications specified in the EU approval, **and**
  - treatment was considered 'promising but unproven' for that individual
- This shift in recruitment would not bias the trial, since treatment groups are balanced on baseline stroke severity by the randomisation system
- Need to increase recruitment. Peter will approach Boehringer to see if they can help with drug supplies in centres where trial has all approvals, but drug supply a problem.
- Suggest a statement for stroke guidelines: 'All patients presenting within 6 hours of acute ischaemic stroke with no clear contraindications for thrombolysis should either be
  - Treated,
  - Or, if they don't exactly meet the terms of the licence, randomised!'

## Plans for disseminating the need for IST-3 to continue

- Slide sets on website
- Webcast (provisionally set for 7th October, details to be confirmed)
- Edit and re-submit comment article to BMJ
- Publish updated Cochrane review
- Collaborators meetings:
  - UK stroke forum, Harrogate December 2008
  - Karolinska Stroke Update Stockholm Nov 17-19<sup>th</sup> 2008
  - Swedish Collaborators, Stockholm January 2009
  - Italian Collaborators, Florence 12-13<sup>th</sup> February 2009
  - Collaborators meeting; ESC Stockholm 26-29<sup>th</sup> May 2009

**THE IST-3  
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## Conclusion

- Updated Cochrane review highlights several questions which remain unanswered, that IST-3 will provide unique data on.
- So far, IST-3 has recruited patients that fall outside the current EU approval
- Continued recruitment in IST-3 of patients that do not meet the terms of the EU approval is
  - ethical
  - very necessary to increase knowledge

## Recent IST3 publications

1. Sandercock P, Lindley R, Wardlaw J, Dennis M, Lewis S, Venables G et al. The third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke. *Trials* 2008;9(1):37.
2. Mangset M, Forde R, Nessa J, Berge E, Wyller TB. "I don't like that, it's tricking people too much...": acute informed consent to participation in a trial of thrombolysis for stroke. *J Med Ethics* 2008 October 1;34(10):751-6.
3. Adam Kobayashi, Joanna M. Wardlaw, Richard I. Lindley, Steff C. Lewis, Peter A. G. Sandercock, Anna Czlonkowska, on behalf of the IST-3 Collaborative Group. Oxfordshire Community Stroke Project clinical stroke syndrome and appearances of tissue and vascular lesions on pre-treatment CT in hyperacute ischaemic stroke among the first 510 patients in the Third International Stroke Trial (IST-3)

## FIRST RANDOMISATION

Our thanks and congratulations go to Dr Frederica Casoni and all the team from Nuovo Ospedale Civile, Modena, Italy for randomising their first patient.

## NEW CENTRES

Our thanks and congratulations go to the following centres for all their hard work in getting through the start-up procedures and are now ready to start randomising:

- Dr Paul Guyler & the team at Southend University Hospital, Southend, UK
- Dr Miguel Branco & the team at Hospital Pero da Covilhã, Covilhã, Portugal
- Dr Gabriela Lopes & the team at Hospital de Santo António, Porto, Portugal
- Professor Philippe Lyrer & the team at Universitätsspital Basel, Basel, Switzerland
- Dr Ahamad Hassan & the team at Leeds General Infirmary, Leeds, UK

We would like to thank Professor Philippe Lyrer, our IST-3 National Co-ordinator in Switzerland for his commitment and great efforts in getting his country started in IST-3.