TESPI (Thrombolysis in Elderly Stroke Patients in Italy)

Svetlana Lorenzano and Danilo Toni on behalf of the TESPI trial Investigators

Objectives

- To evaluate whether treatment with alteplase within three hours of symptom onset in patients with ischemic stroke aged >80 years resulted in improved outcome and favorable benefit/risk ratio compared with standard care.

Methods

- **Design:** Multicenter, open-label, controlled, randomized trial with blinded evaluation of outcome (25 stroke centers in Italy)
- **Randomization ratio:** 1:1
- **Main exclusion criteria:** NIHSS >17 (due to evidence of a steep increase of mortality and decrease of favorable outcome above this score in patients recorded in the Safe Implementation of Thrombolysis in Stroke International Stroke Registry [SITS-ISTR])
- **Primary efficacy endpoint:** favorable functional outcome (modified Rankin Scale score 0-2) at 90 days
- **Key secondary endpoints:** mortality at 90 days and symptomatic intracerebral hemorrhage (SICH) by NINDS definition (any hemorrhage on the 22-36 h post-treatment imaging scan combined with neurological deterioration leading to an increase of ≥1 point on the NIHSS score or leading to death)

Other outcome measures

- Mean/median NIHSS changes from baseline to 2h, 24h, and 7d
- Improvement of ≥4 points or score 0-1 in NIHSS at day 7 from baseline
- Global outcome at day 90 (mRS 0-1, Barthel Index ≥ 95 and Glasgow Outcome Scale 1-2 [good recovery/moderately disabled])
- Stratified endpoint of NIHSS and mRS (baseline NIHSS <8: mRS 0 response; baseline NIHSS 8-14: mRS 0-2 response)

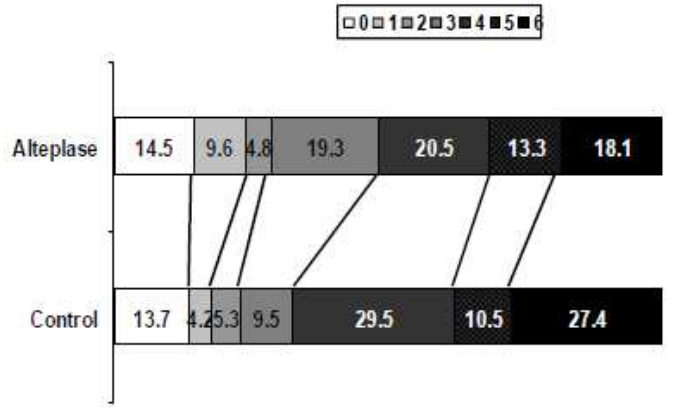
Main results

- The trial was prematurely terminated for ethical reasons after publication of IST-3 trial results which provided evidence of treatment benefit in elderly
- Of the planned 600 patients, a total of 191 (mean [SD] age 85.1 [3.7] years; 61.8% women; 88 assigned to receive alteplase) were enrolled. Approximately 10% of patients (19/191; 9 in the alteplase group) were aged ≥90 years old. Overall, demographic and baseline characteristics, including NIHSS score, were similar between the two groups. Thirteen patients were lost at 90-day follow-up (5 alteplase vs. 8 placebo).

Outcome measures*	Alteplase N=88	Control N=103	*P*
mRS 0-2 at 90 days (%) - Absolute difference - Relative risk (95% CI) - Odds ratio (95% CI)	24/83 (28.9) 5.7% 1.25 (0.76-2.05) 1.35 (0.69-2.64)	22/95 (23.2)	0.381
Death (%)	15/82 (18.3)	26/98 (26.5)	0.189
SICH (NINDS) (%)	5/85 (5.9)	5/98 (5.1)	1.0
NIHSS changes at 24h, mean (SD)	-3.8 (5.7)	-0.8 (6.6)	0.001
NIHSS changes at 7d, mean (SD)	-6.1 (6.6)	-3.8 (6.2)	0.021
NIHSS improvement** at 24h (%)	58/85 (68.2)	54/102 (52.9)	0.034
NIHSS improvement** at 7d (%)	44/86 (51.2)	29/103 (28.2)	0.001

*** Main outcome measures and those resulted as significant; ** ≥4 points or score 0-1**

Distribution of mRS scores at 90 days by treatment group



- Overall, sensitivity analyses (e.g. Per-Protocol analysis and analyses accounting for missing values) and ordinal logistic regression analysis showed consistent results

Conclusions

- TESPI data did not show between-treatment group significant differences in the main outcomes due to the small sample of patients enrolled in the trial, but they would be in favor of efficacy and safety of IV thrombolysis in patients aged ≥ 80 years
- Results evidence a numerically higher proportion of alteplase patients achieving functional independence at 90 days compared to controls (absolute difference of 5.7% compared to 9.6% for over-80 year patients treated within 3h reported in the Cochrane meta-analysis [Wardlaw 2012]) and lower rate of deaths (absolute difference of 8.3% compared to 2.5% in IST-3 based on an approximate calculation on the 672 over-80 year patients recruited within 3h [Lindley 2015]), with SICH rates being similar to controls.
- Alteplase patients had a statistically significant clinical improvement within the initial 7d more frequently than controls suggesting a more effective revascularization/reperfusion from treatment.
  Most of the pre-specified secondary efficacy endpoints consistently indicated that more patients in the alteplase group tended to have a better functional outcome compared to controls
- TESPI trial results are in keeping with those of previous trials, suggesting that in elderly patients compared to standard treatment efficacy and safety of IV thrombolysis given within 3 hours of stroke onset are similar to those reported in younger patients

Study limitations

- Small sample size due to early interruption of the trial. However, after the IST-3 results showed a clearcut evidence of efficacy and safety of IV thrombolysis in patients aged >80 years, it was considered no more ethical continuing to randomize patients in the TESPI trial
- The adoption of NIHSS >17 as an exclusion criteria makes TESPI data not immediately comparable to those of previous trials and may explain the better outcome results observed in the TESPI trial, particularly in comparison with IST-3.