Streptokinase increased mortality in acute ischemic stroke

The Multicenter Acute Stroke Trial—Europe Study Group. **Thrombolytic therapy with streptokinase in acute ischemic stroke.** N Engl J Med. 1996 Jul 18;335:145-50.

Objective
To assess the efficacy and safety of streptokinase in patients who have had an acute ischemic stroke.

Design
6-month, randomized, double-blind, placebo-controlled trial (Multicenter Acute Stroke Trial—Europe [MAST-E]).

Setting
48 French and U.K. centers.

Patients
310 patients (mean age 69 y, 56% men) who were hospitalized with sudden onset of a focal neurologic deficit attributable to ischemia in the region of the middle cerebral artery. Patients had to be randomly assigned within 6 hours of symptom onset. Exclusion criteria were a mild deficit, resolution of symptoms before randomization, cerebral hemorrhage or nonvascular disorder on computed tomography (CT), previous stroke with clinical sequelae, recent surgery or trauma, other serious illness, or pregnancy. Follow-up was complete.

Intervention
Patients were allocated to streptokinase, 1.5 million units (n = 156), or placebo (n = 154); both were given by intravenous infusion for 1 hour. 70% of patients received concomitant treatment with heparin.

Main outcome measures
The primary efficacy outcome combined death and serious disability (Rankin score ≥ 3) at 6 months. Safety outcomes were 10-day mortality and symptomatic and silent intracranial hemorrhage assessed by CT by day 5.

Main results
Analysis was by intention to treat. The groups did not differ for the combined efficacy outcome. Mortality or Rankin score ≥ 3 occurred in 80% of patients who received streptokinase compared with 82% of patients who received placebo ({95% CI for the 2% difference −7% to 11%},* P = 0.60). The 10-day death rate was higher in patients who received streptokinase (34% vs 18%, P = 0.002). {This absolute risk difference of 16% means that over 10 days, 1 additional death occurred for every 6 patients who received streptokinase (compared with placebo), CI 4 to 16; the relative risk increase was 86%, CI 26% to 179%.}* Symptomatic intracranial hemorrhage also occurred more frequently in patients who received streptokinase (21% vs 2.6%, P < 0.001) {absolute risk difference 18.4%, CI additional hemorrhage occurred for every 5 patients who received streptokinase, CI 4 to 8; the relative risk increase was 714%, CI 211% to 2071%}.* The groups did not differ for silent intracranial hemorrhage (45% vs 41%, P = 0.50).

Conclusion
In patients who had acute ischemic stroke, treatment with streptokinase did not improve patient outcomes at 6 months and resulted in increased in-hospital mortality.

Sources of funding: Ministère Français de la Santé; Structure Régionale d'Evaluation Rhône-Alpes; Kabi (streptokinase and placebo).

For article reprint: Dr. M. Hommel, Stroke Unit, Clinique Neurologique, Centre Hospitalier Universitaire de Grenoble, B.P. 217, 38043 Grenoble CEDEX 9, France. FAX 33-76-76-56-31.

*Numbers calculated from data in article.

Abstract and Commentary also published in *ACP Journal Club.* 1997;126:2.

Commentary

The MAST-E study is the fourth medium-sized stroke thrombolysis trial to be reported. It prematurely stopped recruitment at 310 patients (of a planned 600) when safety concerns arose. The results of MAST-E are similar to those reported in MAST-Italy (1), the Australian Streptokinase Trial (2), and the European Cooperative Acute Stroke Study of recombinant tissue plasminogen activator (rtPA) (3) in which thrombolysis was associated with higher rates of early- and late-case fatality but with a lower rate of late disability. These results contrast with those of the National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study (4) that found reduced rates of early and late mortality and late disability. All of the thrombolysis trials showed increased symptomatic intracranial hemorrhage.

The different findings in the NINDS trial and the other thrombolysis trials cannot be easily explained, but differences in treatment delay, dosing, concomitant heparin or aspirin therapy, and stroke severity are probably relevant. For example, patients in the MAST-E study were treated for as long as 6 hours after stroke onset with streptokinase at a myocardial infarction dose, and many received concurrent heparin or aspirin. Patients in the NINDS study were given a submyocardial infarction dose of rtPA within 3 hours of stroke onset and could not receive concurrent heparin or aspirin (4).

These disparate trial results, and the meta-analysis finding of an overall hazard with thrombolysis (5), suggest that further studies are required before streptokinase or rtPA can be recommended for acute ischemic stroke.

Philip Bath, MD
King's College School of Medicine & Dentistry, London, England, UK

References

1. **Multicentre Acute Stoke Trial-Italy (MAST-I).** Lancet 1995;346:1509-14.
2. **Donnan GA, Davis SM, Chambers BR, et al.** Lancet. 1995;345:578-9.
3. **Hacke W, Kaste M, Fieschi C, et al.** JAMA. 1995;274:1017-25.
4. **The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.** N Engl J Med. 1995;333:1581-7
5. **Wardlaw J, Yamaguchi T, del Zoppo G, Hacke W.** The Cochrane Database of Systematic Reviews. 1996; Issue 3.