Streptokinase increased mortality in acute ischemic stroke


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: 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.

Commentary
The MAST-E study is the fourth medium-sized stroke thrombolyis trial to be reported. It is primarily based on reported stroke outcomes at 138 French and U.K. centers (of a planned 600) when safety concerns arose. The results of MAST-E are similar to those reported in MAST-I (1), the Australian Streptokinase Trial (2), and the European Cooperative Acute Stroke Study of recombinant tissue plasminogen activator (r-tPA) (3) in which thrombolysis was associated with higher rates of early- and late-case fatality but with a lower rate of late disability. Those results contrast with those of the National Institute of Neurological Disorders and Stroke (NINDS) r-tPA Stroke Study (4) that found reduced rates of early and late disability. All of the thrombolysis trials showed increased symptomatic intracranial hemorrhage. The different findings in the NINDS trial and the other thrombolyis trials cannot be easily explained, but differences in treatment delay, dosage, concurrent aspirin or other antiplatelet 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 aspirin or heparin. Patients in the NINDS study were given a sublytic myocardial infarction dose of r-tPA within 3 hours of stroke onset and could not receive concurrent aspirin or heparin (6).


did not improve patient outcomes within 6 months and resulted in increased hospital mortality.


Design
Randomized controlled trial (Stroke Prevention in Atrial Fibrillation [SPAF] III) that was stopped after a mean follow-up of 1.1 years.

Setting
20 clinical centers in North America.

Patients
1044 patients (mean age 72 y, 61% men) with current or recurrent nonvalvular atrial fibrillation and at least 1 thromboembolic risk factor. Exclusion criteria were prosthetic heart valves; mitral stenosis; other conditions that required anticoagulation therapy; or contraindication to aspirin or warfarin. No patients were lost to follow-up.

Intervention
521 patients were allocated to low-intensity, fixed-dose warfarin (0.5 to 3.0 mg/d) (to raise the international normalized ratio [INR] to between 1.2 and 1.5), plus aspirin, 325 mg/d. The fixed-dose of warfarin was not adjusted, whereas the INR target was 2.0 to 3.0 for those receiving adjusted-dose warfarin. The initial dose was based on the patient's age and then adjusted to stabilize the INR between 2.0 and 3.0.

Main outcome measures
Ischemic stroke, systemic embolism, transient ischemic attack, myocardial infarction, major hemorrhage, and death.

Main results
The mean INR in patients receiving combination therapy was 1.3 compared with 2.4 for those receiving adjusted-dose warfarin. 44 patients (7.9%) receiving combination therapy had an ischemic stroke or systemic embolism compared with 11 patients (1.9%) receiving adjusted-dose warfarin (P = 0.001). This absolute risk difference of 6% means that for a mean of 1.1 years, 1 additional isch