Improving Outcome After Stroke
Time to Treat New Targets

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A clinically meaningful improvement in stroke outcome is the primary measure for developing effective new treatments. So far, only thrombolysis, hemicraniectomy for malignant infarction, and stroke unit care are evidence-based therapies for ischemic stroke that achieve this goal with a substantial and long-lasting effect on neurological outcome.1 Besides the initial ischemic event, several factors including age, pre-existing comorbidities, and poststroke complications determine the final clinical outcome.2 Particularly, poststroke complications affect morbidity and mortality.2 Frequent problems include epileptic seizures, depression, central pain, obstructive sleep apnea, cognitive dysfunction, and medical complications such as respiratory and urinary tract infections as well as cardiac arrhythmias.2–4 An early diagnosis with subsequent adequate treatment of these complications was assumed to improve outcome after stroke.5 Recent studies suggest in principle that prophylactic treatment (before its occurrence) of such poststroke complications might be even more beneficial than starting a treatment once a diagnosis of a specific complication is made. If true, such an acute prophylactic treatment of poststroke sequelae may have an enormous impact on the improvement of long-term neurological outcome and could become an important part in the care of patients with stroke besides acute treatment and secondary prevention. In this editorial, we highlight that for several poststroke complications, a targeted prophylactic approach involving treatment of patients who are at high risk of developing this specific complication might be particularly appropriate to improve stroke outcome.

Depression is a frequent complication after stroke with a prevalence of up to 50%. Poststroke depression is associated with impaired neurological recovery and increased mortality. Antidepressive therapy has been demonstrated to be beneficial for treating poststroke depression and to reduce the incidence of depression in nondepressed patients with stroke.5,6 Pharmacotherapy before the occurrence of depression might even improve the overall outcome after stroke. This prophylactic approach was recently investigated in a pilot study. The Fluoxetine for Motor Recovery After Acute Ischaemic Stroke (FLAME) trial showed that antidepressive treatment in nondepressed patients with stroke not only prevents depression, but moreover improves motor recovery and the overall neurological outcome.7 In this double-blind trial, 118 nondepressed patients with ischemic stroke were randomly assigned to receive either fluoxetine or placebo for 3 months starting between 5 and 10 days after the onset of stroke. Functional outcome as measured by the change on the Fugl-Meyer motor scale and by the modified Rankin Scale was significantly improved in fluoxetine-treated patients compared with placebo patients. A reduced frequency of depression under fluoxetine compared with placebo treatment suggests that enhancing mood at least partly contributes to the improved overall outcome. Although these results must be replicated in a larger trial, antidepressive treatment may represent an option to improve outcome of a wide range of patients with stroke. However, further studies using other antidepressants are needed to evaluate whether antidepressive effects or specific properties of fluoxetine such as its anti-inflammatory actions account for the improved recovery in the FLAME trial.

Up to 40% of patients with stroke develop infections and these in turn are associated with poor outcome.8,9 Prophylactic antibiotics poststroke were shown to lower the frequency of infections. However, results on functional recovery of studies using this approach are conflicting. On comparing mezlocillin plus sulbactam with placebo, Schwarz and colleagues report an improved clinical outcome after verum treatment.10 Although promising, these results must be interpreted with caution because treatment allocation was not concealed to the treating physicians and this study was not powered to detect clinical outcomes. The larger Preventive Antibacterial Therapy in Acute Ischemic Stroke (PANTHERIS) study used moxifloxacin for antibiotic therapy.11 Despite a reduced infection rate (per protocol analysis) compared with placebo patients. A reduced frequency of infections. However, results on functional recovery of studies using this approach are conflicting. On comparing mezlocillin plus sulbactam with placebo, Schwarz and colleagues report an improved clinical outcome after verum treatment.10 Although promising, these results must be interpreted with caution because treatment allocation was not concealed to the treating physicians and this study was not powered to detect clinical outcomes. The larger Preventive Antibacterial Therapy in Acute Ischemic Stroke (PANTHERIS) study used moxifloxacin for antibiotic therapy.11 Despite a reduced infection rate (per protocol analysis) in the treatment group and a significant association between infections and survival, no beneficial effects of prophylactic moxifloxacin administration on mortality or functional outcome were observed. However, for conclusive results on the efficacy of prophylactic antibacterial treatment, larger studies are needed. Currently a Phase III trial is underway to investigate ceftriaxone for antibiotic prophylaxis in 3200 patients.12 The success of future studies on prophylactic antibiotics after stroke might be increased when only patients at high risk for infectious complications are considered. Established risk factors for poststroke infections include dysphagia, large infarcts, and monocytic HLA-DR expression.8,11,13 Sleep-related breathing disorders such as obstructive and central sleep apnea are also relevant complications in the
early phase after stroke occurring in up to 72% of all patients with stroke. Hypercapnia due to sleep apnea is assumed to contribute to early neurological deterioration by causing cerebral vasodilatation in arteries unaffected by ischemia with a subsequent steal of blood from ischemic and peri-ischemic areas of the brain. Continuous positive airway pressure (CPAP) therapy is the treatment of choice for sleep-related breathing disorders. CPAP therapy improves neurological outcome and may reduce the mortality of patients with stroke with obstructive sleep apnea. So far studies on CPAP therapy were mainly performed in the chronic phase after stroke in patients with diagnosed sleep apnea for the secondary prevention of hypertension and subsequent strokes. CPAP therapy, however, might be beneficial as “acute prophylactic” treatment in the first night after stroke because hemodynamic disturbances due to sleep apnea have markedly detrimental effects at this stage. Results of a current Phase I/II study that investigates the feasibility and efficacy of CPAP therapy for prophylactic treatment in patients with acute stroke without diagnosed sleep-related breathing disorders are expected soon (NCT00151177). Factors associated with a sleep-related breathing disorder after stroke such as higher age, male gender, an increased body mass index, and previous stroke should be considered as inclusion criteria for future trials of prophylactic CPAP treatment.

Cognitive impairment is another target for prophylactic therapy after stroke. Approximately 10% of all patients with stroke newly develop dementia with the risk of dementia increasing at an average rate of 3% per year after a stroke. So far, prevention of poststroke dementia by blood pressure-lowering drugs is the only treatment proven to reduce the risk of poststroke dementia. However, the effects of antihypertensive therapy seem primarily to be mediated by the prevention of recurrent stroke rather than to specific effects on cognitive functions. Preliminary results of a clinical trial on citicoline, an intermediate in membrane phospholipid synthesis and an acetylcholine precursor, suggest that prophylactic treatment might have the potential to reduce the risk of poststroke cognitive impairment. However, for conclusive results, the final publication of this trial needs to be awaited.

In conclusion, prophylactic interventions for poststroke complications represent a promising approach to improve the overall neurological outcome of patients with stroke in the long run. So far, the best evidence for this concept exists for antidepressive treatment of nondepressed patients with stroke. A better understanding of which patients are at risk to develop specific poststroke complications may allow an individually tailored prophylactic treatment. Disclosures

W.-R.S. received honoraria for several presentations on citicoline from Trommsdorff.

References


Key Words: complications ■ prophylactic treatment ■ stroke
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Stroke. 2012;43:295-296; originally published online December 22, 2011;
doi: 10.1161/STROKEAHA.111.642363

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/43/2/295

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