Emerging Therapies for Cerebrovascular Disorders

Marc Fisher, MD; Antonio Davalos, MD, PhD

New information about therapeutic interventions regarding several important aspects of cerebrovascular disease has appeared recently. This short review will focus on new therapeutic developments concerning the prevention of ischemic stroke, acute ischemic stroke therapy trials, and, lastly, the management of patients with intracranial aneurysms.

Great strides have been made in the pharmacological management of patients to reduce the risk for developing ischemic stroke. Stroke prevention is now clearly a multimodal endeavor that encompasses not only the use of antithrombotic agents but also the identification and treatment of multiple, potential stroke risk factors. While the precise relationship of elevated total and LDL cholesterol to stroke risk remains to be determined, prior studies clearly demonstrated substantial primary stroke risk reduction with the use of various statins in patients with cardiovascular disease. A recent report by the Heart Protection Study Collaborative Group (HPS) suggests that the benefits of at least 1 statin, simvastatin, extend to stroke patients as well. In this study, 20,536 patients with 1 form of vascular disease or diabetes mellitus were randomized to 40 mg of simvastatin daily or placebo in addition to their baseline medications and followed on average for 5 years. Of patients randomized, 1820 had stroke alone and 1460 had stroke and coronary artery disease. Allocation to simvastatin was associated with an overall 25% reduction in first stroke. Patients with stroke in the study had a similar benefit for subsequent major vascular events, although precise characterization of risk reduction for secondary stroke was not provided. The results may in fact underestimate the benefits of simvastatin because on average 17% of placebo allocated patients took a nonstudy statin. The result of this study led to a change in the indications for simvastatin by the FDA, and the medication is now indicated in stroke patients, ie, secondary prevention. Another recent study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), provided additional information about primary stroke risk reduction and potentially secondary risk reduction with atorvastatin. In this study, 10,305 hypertensive patients with moderate baseline cholesterol levels and vascular disease or other vascular risk factors received 10 mg of atorvastatin or placebo for a mean 3.3 years. Approximately 10% of the allocated patients had a history of stroke or TIA. The atorvastatin group had a 36% relative risk reduction for the primary end point of nonfatal or fatal coronary heart disease and a 27% relative risk reduction for nonfatal or fatal stroke. A separate analysis of the patients with prior stroke was not provided. This study does demonstrate that modest atorvastatin therapy reduces stroke risk in hypertensive patients with mild cholesterol elevations with a variety of vascular risk factors.

The benefits of angiotensin converting enzyme (ACE) inhibitors on stroke prevention in normotensive and hypertensive patients with other vascular risk factors are established. Two new reports suggest better functional outcome in patients who suffer a primary or recurrent stroke treated with these drugs. A detailed analysis of the impact of ramipril on stroke and the related disability in the HOPE study appeared recently. This trial randomized 9541 patients with 1 form of vascular disease or diabetes mellitus plus 1 additional risk factor to ramipril, 10 mg daily or placebo, with an average follow-up of 4.5 years. The relative risk of fatal and nonfatal strokes was reduced by 32% (156 versus 226) in the group treated with ramipril compared with placebo, associated with a modest decrease of blood pressure (3/2 mm Hg). Significantly fewer patients on ramipril had cognitive or functional impairment at day 7 after stroke. New data demonstrated a better long-term functional outcome in patients treated with perindopril as well. In the PROGRESS study, 6105 patients with previous non–major disabling stroke or TIA were randomized to 4 mg daily of perindopril alone or in combination with indapamide (2.5 mg) or placebo during a median follow-up of 4 years. Active treatment reduced the odds of disability by 24%, and the odds of dependency by 16%, at the last available assessment due largely to a reduction in recurrent stroke. The effect was more consistent with the combination therapy and appeared to be similar in hypertensive and normotensive patients.

The benefit of ACE inhibitors in reducing cardiovascular events in individuals with hypertension has been documented over the past decade; however, their relative value compared with older, less-expensive antihypertensive agents remains unclear. The ALLHAT study recently addressed this issue in patients with a history of hypertension and at least 1 additional cardiovascular risk factor. A total of 33,357 patients were randomly assigned to receive chlorthalidone 12.5 to 25 mg/d, amlodipine 2.5 to 10 mg/d, or lisinopril 10 to 40 mg/d to achieve a goal blood pressure <140/90 mm Hg. During a mean follow-up of 4.9 years, the target blood pressure was more frequently achieved in the chlorthalidone group. Allocation to chlorthalidone was associated with a 10% risk reduction of combined cardiovascular disease and with a 15% risk reduction of stroke in comparison with lisinopril, al-

© 2004 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org
DOI: 10.1161/01.STR.0000115296.67346.28
though these effects were statistically significant only in blacks. No differences in cardiovascular events or stroke prevention were seen in comparison with amldopine. Chlorothalidone reduced the risk of heart failure in comparison with lisinopril and amldopine. This study demonstrates that a thiazide-type diuretic was at least as effective or superior to more expensive drugs in preventing major cardiovascular events in high-risk hypertensive patients.

Two recent developments in acute ischemic stroke therapy may help to expand the therapeutic time window. Abciximab, a long-acting platelet glycoprotein IIb/IIIa antagonist, and desmoteplase, a new thrombolytic agent with a long life and fibrin selective action, demonstrated promising results in phase IIb trials. The AbESTT study randomized 400 patients within 6 hours of onset of ischemic stroke to abciximab 0.25 mg/kg in bolus followed by a 12-hour infusion at 0.125 µg/kg per minute or placebo. A few patients were treated within 3 hours, and approximately 50% of patients were treated from 3 to 5 hours after onset. The drug showed a reasonable safety profile, as symptomatic intracranial hemorrhage was diagnosed in 3.6% of patients treated with abciximab and in 1% of the placebo group. Favorable outcome at 3 months, defined as a modified Rankin Scale (mRS) 0 or 1, was achieved by 48.5% of patients in the abciximab group and by 40% in the placebo group (P=0.087). In a prospective mRS responder analysis at 3 months as a function of baseline stroke severity, abciximab had an odds ratio of favorable outcome of 1.55, CI 1.02 to 2.38 (P<0.05). Post hoc analysis in patients treated within 5 hours revealed a significant and more consistent response to abciximab in terms of favorable outcome, neurological recovery, and functional independence in daily living activities. This study suggests possible efficacy of abciximab in acute stroke, with a longer therapeutic window and a better safety profile than tissue plasminogen activator (tPA) within 3 hours. A large phase III study (AbESTT-II) is under way to confirm these findings.

The recently completed phase II-B DIAS (Desmoteplase in Acute Stroke) study of a tPA molecule derived from bat saliva used diffusion/perfusion MRI to enroll patients and to assess the biological activity of different doses. Patients were included in the study between 3 to 9 hours after stroke onset if they demonstrated a perfusion lesion volume ≥20% above the baseline diffusion lesion volume. Magnetic resonance angiography was also performed and all 3 MRI modalities were repeated several hours after completion of the thrombolytic therapy to evaluate reperfusion efficacy. Initial doses of non-weight-adjusted desmoteplase derived from prior myocardial infarction studies proved to have an unacceptably high rate of intracerebral hemorrhage. Lower, weight-adjusted dosing demonstrated a very reasonable safety profile and quite dramatic reperfusion efficacy, as compared with vehicle treated patients (W. Soehngen, MD, personal communication, November 15, 2003). Clinical outcome tended to be more favorable in treated patients as well. This preliminary study is important because it confirms the safety of weight-adjusted desmoteplase in ischemic stroke patients when given up to 9 hours after stroke onset and that safe doses have the intended biological effect of inducing reperfusion. A pivotal efficacy study is currently being planned and it is hoped will begin soon.

The management of patients with unruptured and ruptured intracranial aneurysms remains challenging, and a recent study provided important new information to help clinicians in this therapeutic area. The natural history and results of surgical/endovascular interventions for unruptured aneurysms was addressed by the recent report from the International Study of Unruptured Aneurysm Investigators. In a prior report, this study group retrospectively evaluated the natural history of aneurysms and prospectively assessed the risks of surgical repair. In the current report, both issues were evaluated prospectively and some of the patients undergoing intervention were treated endovascularly. The study evaluated 4060 with an angiographically confirmed intracranial aneurysm. The clinicians involved made management decisions. A total of 1917 patients underwent microsurgical aneurysm clipping, 451 an endovascular procedure, and 1692 had no intervention. Patients were further characterized into 2 groups: group 1 included those without a history of prior subarachnoid hemorrhage (SAH), and group 2 consisted of those with such a history. The risk of rupture was very small in both groups with aneurysms <7 mm over a period of 4.1 years. The risk of rupture over 5 years in group 1 patients with an anterior circulation aneurysm increased in relationship to baseline aneurysm size and was 2.6% for aneurysms of 7 to 12 mm, 14.5% for 13 to 24 mm, and 40% for ≥25 mm. Posterior circulation aneurysms for group 1 patients demonstrated a similar size to risk of rupture relationship. In group 2 patients with a history of prior aneurysm rupture, there were very few patients with aneurysms >12 mm, and the relationship of subsequent risk of rupture to aneurysm size was not obvious. In addition to aneurysm size in patients without prior rupture, multivariate analysis identified 3 aneurysm locations (basilar tip, cavernous carotid, and posterior communicating) as being associated with increased risk for hemorrhage. For patients undergoing surgery or endovascular therapy, 1-year procedure related mortality was similar and overall morbidity and mortality was slightly higher in the surgically treated patients. These results provide useful information for clinicians evaluating patients with unruptured aneurysms but must be viewed cautiously. The selection of patients included in the study may have been biased and likely do not represent the complete spectrum of patients with unruptured aneurysms. The procedure related complication rates are higher than reported in previously reported retrospective series and do not truly address the issue of how surgical and endovascular therapy compare.

References


**Key Words:** Advances in Stroke ■ aneurysm ■ cerebrovascular disorders ■ prevention ■ therapy
Emerging Therapies for Cerebrovascular Disorders
Marc Fisher and Antonio Davalos

Stroke. 2004;35:367-369
doi: 10.1161/01.STR.0000115296.67346.28
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
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/35/2/367

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/