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## Advances in Stroke 2007: introduction

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# Stroke

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## Introduction

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## Advances in Stroke 2007

### Introduction

Marc Fisher, MD

The annual update of a broad range of topics related to cerebrovascular diseases encompassed by the designated sections of *Stroke* is a widely appreciated feature. The current update was expanded from previous years to now include the new section of Population Studies, and additionally the basic science editors invited 2 updates with relevance to both basic scientists and clinicians. The editors hope that the readership will continue to value these brief but insightful updates and provide feedback as to how to potentially improve the material encompassed in the annual Advances section. We thank the section editors and the basic science contributors for their efforts.

In the genetics area, many important studies appeared using genome-wide associations with a variety of complex medical disorders. However, such a study of ischemic stroke did not demonstrate that a single locus of main effect could be determined. Genetic associations of single nucleotide polymorphisms are also becoming increasingly common. We can anticipate further studies of both types in helping to elucidate genetic contributions to a variety of cerebrovascular disorders.

Acute stroke therapies had another disappointing year with failure of the neuroprotective drug NXY-059 in a second, large phase III trial reported initially in late 2006 and in more detail subsequently. Additionally, the novel thrombolytic agent, desmoteplase, that had initially shown promise in 2 very small early phase II trials did not demonstrate benefit in a larger study presented at the 2007 European Stroke Conference. The reasons for this failure remain obscure and may be clarified after detailed publication of the trial results.

The stroke prevention area was a therapeutic bright spot in comparison to the predominantly gloomy results from acute therapy trials. A trial of oral anticoagulation in elderly nonvalvular atrial fibrillation patients demonstrated that warfarin was superior to aspirin with no increase in serious bleeding side effects. A study from the United Kingdom of urgent outpatient clinical assessment after transient ischemic attack revealed that this approach substantially reduced stroke risk as compared with routine evaluation by primary care physicians. The use of the ABCD<sup>2</sup> scoring scale for identifying low and high risk transient ischemic attack patients was confirmed, and this approach will likely prove useful in future acute intervention studies after transient ischemic attack.

An important advance in the critical care management of ischemic stroke patients in 2007 was the publication of the combined evaluation of 3 small hemicraniectomy trials for patients with malignant middle cerebral artery infarction. The pooled analysis demonstrated a very substantial benefit for this surgical approach as compared with standard medical therapy for improving survival without an increase in dependency. The restricted nature of the patient population studied leaves many unanswered questions that will hopefully be addressed by future trials. A disappointment in 2007 was the failure of recombinant factor VII to improve outcome in patients with intracerebral hemorrhage, despite a beneficial effect on hemorrhage growth in a phase III trial. Subgroup analysis of the study suggested that a select group may benefit, but it is unclear whether further trials are forthcoming.

Healthcare policies continue to impact the care of cerebrovascular patients. Proposals for improving care were provided by several national and international groups, along with new and updated guidelines. The utility of stroke units was confirmed and more widespread availability should be encouraged. The use of predictive modeling and enhancement of quality improvement are other areas that should lead to improved care.

In 2007 more information appeared about interventional procedures for cerebrovascular disorders. Several important studies of carotid artery stenting were published, but a definitive comparison with endarterectomy remains lacking. A stent for intracranial atherosclerosis was approved for use by the FDA, and registry data suggest efficacy in reducing stenosis with a reasonable complication rate.

Imaging of the ischemic penumbra with diffusion/perfusion MRI and perfusion CT was evaluated in several publications. Case series suggest that such penumbral imaging with MRI may be useful for selection of patients for thrombolysis beyond 3 hours. A direct comparison of CT and MRI penumbral imaging remains lacking, but both were performed in the unsuccessful DIAS-II study of desmoteplase, so information about comparable use should be forthcoming. Multimodal MRI studies may also be useful in predicting hemorrhagic risk with thrombolysis, but larger confirmatory studies are needed.

The area of brain recovery and rehabilitation was heartened by the reports that widely available fibroblasts can be used to

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produce multipotential embryonic stem cells. Although this is an important advance, the potential of any type of stem cells to enhance stroke recovery remains unproven. The beneficial effects of stem cells may be related primarily to related growth factors and cytokines, some of which are currently under investigation as recovery enhancing agents. Imaging is also of increasing use in relationship to stroke recovery, and functional MRI and PET studies are being used to assess recovery enhancing therapies. Preliminary interesting studies of transcranial magnetic stimulation and local electrical stimulation of muscles suggest that larger studies are warranted.

The relationship of vascular disorders to dementia continues to be strengthened by newer studies. The risk of dementia was reported to be increased 4-fold in patients with subcortical infarcts. Cortical microinfarcts and microbleeds were also shown to be associated with cognitive decline. A study of galantamine in patients with probable vascular dementia demonstrated that this cholinesterase inhibitor improved cognition and executive function but did not improve activities of daily living. As in other areas, imaging advances are helping to assess patients with vascular cognitive impairment, and the most interesting imaging modalities appear to be diffusion tensor imaging and fractional anisotropy.

The 3 new contributions to the Advances in Stroke for 2007 include the new section, Population Studies, and 2 translation-related contributions. Population-related studies indicated an increase in stroke hospitalization for 45- to 54-year-olds over the past 2 decades and a general increase in

inflation-adjusted cost for stroke-related diagnoses. Links between air pollution, the metabolic syndrome, socioeconomic status and stroke were enhanced by other studies.

Understanding of the mechanisms of neuronal death in relationship to ischemia continued to evolve in 2007. The important contributions of PARP1 activation and apoptosis-inducing factor release as mediators of programmed cell death became clearer. The role of mitochondrial death-inducing signals such as BNIP3 also was clarified. Stress induction of the endoplasmic reticulum, leading to autophagy may also be an important mediator of ischemia-related cell death. Translating enhanced basic understanding of ischemia-related brain tissue injury into potential novel therapies is an increasingly important endeavor. High-flow 100% normobaric hyperoxia prolongs penumbral survival in animals and appears to extend the time window for reperfusion therapy. One small feasibility study of this therapeutic approach demonstrated safety and possible efficacy. Other gases, such as hydrogen, helium and xenon, also demonstrate efficacy in animal models. Laser light energy may improve stroke outcome, and ultrasound energy may enhance clot dissolution by tissue plasminogen activator.

As has been typical in the cerebrovascular arena, 2007 was marked by many advances and disappointing clinical trial failures, but the effort to move the field forward continues unabated and with increasing energy, resources and manpower.

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KEY WORDS: advances ■ stroke