

Ischemic Stroke

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Ischemic stroke is a disorder of altered hemostasis. Attempts to limit the neurological consequences involve the use of anti-thrombotic agents or the use of agents that could limit the impact of ischemic injury on neurons and glia. Recent years have seen concerns raised about the ability to successfully perform Phase III interventional trials based on the experience with neuron protective agents, and concerns about the limitations of translation between experimental models and the condition of stroke in humans. A resurgence of interest in examining later treatment with plasminogen activators *in the acute setting* has further refined the clinical need. In this presentation, we will discuss new information about acute treatment with recombinant tissue plasminogen activator (rt-PA), new data regarding the management of secondary prevention with specific anti-platelet agents, and new fundamental research work that addresses our understanding of how specific components of the coagulation and plasminogen activator-plasminogen systems can mediate non-vascular processes in the central nervous system (CNS).

In response to an official request from the regulatory agency in Europe, a phase III, double-blind, placebo-controlled study of rt-PA in patients treated with ischemic stroke 3.0 - 4.5 hours following symptom onset has been undertaken and completed (ECASS III). ECASS III demonstrated a significant improvement in best outcome (modified Rankin score [mRS] = 0-1) among patients treated with rt-PA in this interval. Patients entered into the trial were the subject of strict criteria that excluded individuals with microvascular disease and chronic illness (i.e. diabetes and hypertension), potentially at risk for CNS hemorrhagic events. The provocative implication is that patients can be treated later than the 3.0 hour period of intervention. However, advisory statements emphasize the need for immediate treatment. This recalls clinical trial and experimental work of some 20 years previously that included patients in these intervals with evidence of individual patient improvement. Criteria for defining patient subpopulations and their risk following exposure to rt-PA would be quite valuable.

Secondary prevention of recurrent ischemic stroke following a primary event has been the subject of ongoing clinical interest. Published guidelines indicate the value of the combination of aspirin-dipyridamole, aspirin alone, or clopidogrel under specific conditions. The bases for these recommendations have been much discussed, and have led to a head-to-head (non-inferiority) comparison of the combination aspirin (ASA)-extended release dipyridamole (ERDP) against clopidogrel, with or without the ARP telmisartan, by 2x2 factorial design, in a large cohort study. The Prevention Regimen for Effectively Avoiding Second Strokes (ProFESS) trial was completed in 2008. It found no difference between the use of the combination ASA-ERDP and clopidogrel in the prevention of recurrent events. The results of this study have led to much discussion about the interpretation. But, clinical practice guidelines do not yet reflect a change at this writing. For primary prevention of thromboembolic events in patients with atrial fibrillation, recent work has indicated the non-inferiority of percutaneous closure of the atrial appendage to the use of warfarin (2:1 randomization), although the frequency of safety events in the interventional arm exceeded those in the warfarin (control) arm. Guidelines for the use of oral anticoagulation to reduce the risk of an ischemic, or systemic embolic event, still hold.

Parallel and ongoing fundamental research work expands our understanding of how specific components of hemostasis can affect non-vascular processes in the CNS during ischemia and trauma. Evidence from experimental focal ischemia model studies and cell culture experiments indicate that rt-PA can under certain circumstances cause neuron injury or demise. Fundamental studies have clearly demonstrated that thrombolysis and recanalization in animal models can significantly reduce injury volumes, and very early intervention does not increase the risk of CNS hemorrhage. Additional *in vitro* studies have demonstrated *in vitro* that similar concentrations of rt-PA

can injure endothelial cells directly. While the study results have led to much speculation about their clinical significance, recent work has proceeded along two lines: i) the demonstration that certain plasminogen activators are used in the CNS for non-hemostatic purposes, and ii) the relevance of rt-PA concentration/dosage to the outcomes observed.

Both at the clinical and experimental level recently reported work about acute treatment strategies and the potential roles of hemostasis in the management of ischemic brain injury provide evidence that anti-thrombotic agents continue to play a prominent role in the treatment of ischemic stroke. Future work should serve to understand better the individual patient risks involved with both exposure to agents that can modulate thrombotic disease, as well as hemorrhagic risk.