The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial: Results of the Vanguard Phase

A number of observational studies have shown that the risk of a poor outcome after acute intracerebral hemorrhage (ICH), including early death, is greater among patients who present with higher blood pressure (BP). For every 1–2 mm Hg increase in systolic BP (SBP) there is approximately a 1% increase in death and dependency. However, the effects associated with early lowering of BP are less clear.

Prof. Craig Anderson, Stroke Medicine and Clinical Neuroscience, Royal Prince Alfred Hospital, Sydney, Australia, presented results from the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT). This was an open-label, pilot phase, randomized controlled trial that enrolled 404 patients from 44 hospitals in Australia, China, and Korea from November 2005 to April 2007. Patients ≥18 years with SBP of 150-220 mm Hg were assigned to receive a treatment strategy of either intensive BP lowering (target SBP 140 mm Hg) based on a stepped protocol of routinely available intravenous agents or the 1999 American Heart Association (AHA) guideline-based BP lowering (target SBP 180 mm Hg within 6 hours of ICH. ICH was confirmed by computerized tomography (CT) scan. The primary outcome was proportional growth in hematoma volume on repeat CT at 24 hours. Clinical outcomes and adverse events were assessed over 90 days.

SBP was an average of 14 mm Hg lower (p<0.0001; Figure 1) in the intensive BP lowering group compared with patients in the AHA guideline group at 1 hour post-randomization. Mean proportional hematoma growth was 22.6% lower (95% CI 0.6–44.5%; adjusted p=0.06) in the intensive group compared with the guideline group (36.3 mL vs 13.7 mL), after adjustment for initial hematoma volume and time from ICH to CT. This equated to about 2 mL less blood in the brain associated with early intensive BP lowering (Table 1.) Likewise, 'substantial' hematoma growth (ongoing bleeding >33% or 12.5 mL) was 36% (95% CI 0–59%; p=0.05; Table 1) lower in the intensively managed group. There was no evidence of differences in type or frequency of serious adverse events between the two treatment approaches or in clinical outcome at 90 days.

Figure 1. Mean (95% CI) Systolic BP Differences.

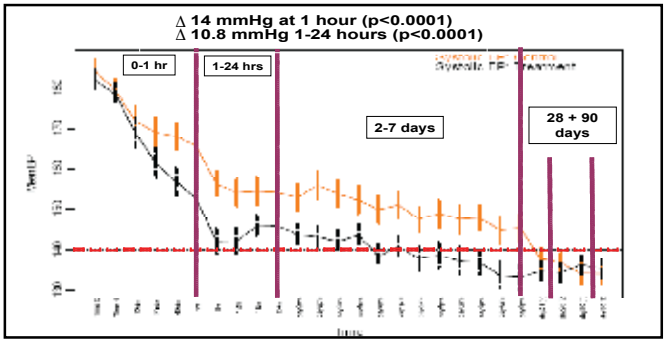


Table 1. Indices of Hematoma Growth.

	Standard (n=172)	Intensive (n=174)	Difference (95% CI)	p
Mean of % increases, %	36.3	13.7	22.6 (-0.6 to -44.6)	0.06
Mean absolute increase, ml	2.7	0.9	1.7 (-0.5 to 4.0)	0.13
Substantial growth, % (>33% or 12.5 ml)	23	15	8 (-1 to 17)	0.05
Relative risk reduction			36 (0 to 59)	

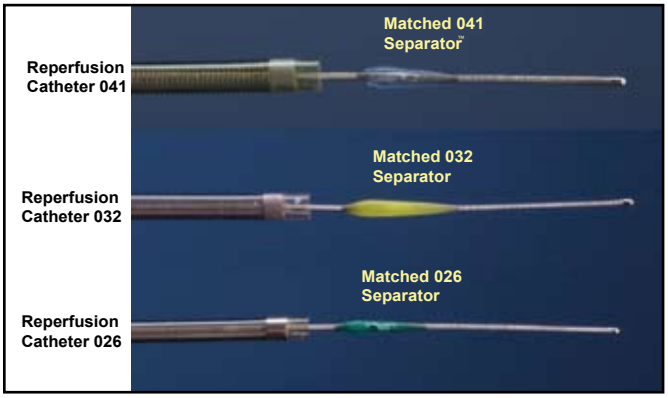
*Analyses adjusted for baseline hematoma volume and time from onset to CT scan; proportional and absolute changes analyzed by linear regression and 'substantial' growht by logistic regression
**Similar results with no adjustment, and with adjustment for rFVIIa use

The results of the INTERACT study show that early intensive blood pressure lowering with careful monitoring is feasible, safe, and well tolerated, and appears to produce a modest attenuation of bleeding and hematoma growth in ICH. Because antihypertensive agents are inexpensive and widely available, widespread adoption of BP lowering could translate into high absolute benefits. A large-scale trial powered to evaluate clinical endpoints is planned to commence later this year.

The Penumbra Stroke Trial

Currently, the only approved treatments for thromboembolus in acute stroke are the thrombolytic agents such as tPA. However, clot-removing drugs have a high risk of bleeding complications, and they are not as effective in patients with severe strokes. The Penumbra System is a novel mechanical device designed to remove stroke-associated occlusions from the large brain vessels and is approved for use in acute stroke. The system comprises an aspirating reperfusion catheter, a separator for clearing, and a thrombus removal ring that is designed to capture calcified, hard clots (Figure 1).

Figure 1. Aspiration System.



Cameron McDougall, MD, Barrow Neurological Institute, Phoenix, AZ, reported results from an international multi-center study that was conducted in 125 stroke patients with occluded vessels. The objective of the trial was to assess the safety and the revascularization effectiveness of this novel clot removal system. Patient inclusion criteria included NIH Stroke Scale (NIHSS) score ~8, presentation within 8 hours of symptom onset, and a Thrombolysis in Myocardial Infarction (TIMI) score of 0 or I. The primary endpoints were TIMI score II or III and device-related serious adverse events (SAE). Secondary endpoints included ≥4 point improvement on the NIHSS at discharge or modified Rankin Scale (mRS) ≤2 at 30 days, all cause mortality, and incidence of intracranial hemorrhage (ICH).

The median time from symptom onset to procedural start was 4.1 hours; the median time required for revascularization was 45 minutes. Using the Penumbra System, 82% of the treated vessels were revascularized to TIMI II or III, with 41.6% of the patients having a favorable outcome at 30 days. None of the SAEs (3%; 2 perforations; 2 ICHs) was device-related. A total of 35 patients (28%) were found to have ICH at 24 hours, of which 14 (11.2%) were symptomatic (CT evidence of a bleed and a 4-point drop on the NIHSS) and 21 (16.8%) were asymptomatic. At the time of discharge, 58% of the patients had a ≥4 point improvement in NIHSS, and 27% had a ≥10 point improvement in NIHSS or NIHSS 0-1. All cause mortality was 26.4%, and 32.8%, respectively, at 30 and 90 days; 25% of patients had a 90-day mRS of ≤2. Due to the effectiveness of the initial aspiration, direct thrombus extraction was used in only 30 of 125 patients.

The Penumbra System was associated with a low rate of serious procedural complications and had an acceptable rate of ICH and all cause mortality. The trend for a better outcome when vessels were opened was consistently observed across all neurological and functional measures.

The US Food and Drug Administration granted clearance of the Penumbra System for revascularization of intracranial vessels in patients with acute ischemic stroke in December 2007. The retrieval ring was used in a minority of patients, and as a result, it was not felt to have been adequately evaluated and therefore was not approved. No complications or adverse events occurred as result of the use of the retrieval ring.

Donepezil in Subcortical Vascular Cognitive Impairment: A Randomized Double-Blind Trial in CADASIL

Cholinergic inhibitors have been shown to provide benefits in cognition, global functioning, and activities of daily living in patients with mild to moderate Alzheimer disease (AD). However, their benefit in cognitive impairment associated with vascular dementia (VaD) remains controversial. One of the limitations of past studies using cholinergic inhibitors has been the inability to determine whether the treatment was affecting AD or VaD. Thus, there is a need for trials involving more narrowly defined subtypes of VaD. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an early-onset genetic form of subcortical ischemic vascular dementia that resembles sporadic small-vessel disease similar to VaD. The underlying pathology of CADASIL is progressive degeneration of the smooth muscle cells in blood vessels that can lead to deficits in executive functioning and cognitive processing speed.

Prof. Martin Dichgans, Ludwig-Maximilians-University, Munich, Germany, presented data from an 18-week, double-blind, placebo-controlled, multi-national study evaluating the efficacy and safety of donepezil (10 mg), a cholinesterase-inhibiting drug currently approved for the treatment of AD, in 168 patients diagnosed with CADASIL. Changes in cognitive impairment were assessed using a number of tests, including the vascular AD assessment cognitive subscale (V-ADAS-cog), the mini-mental state examination (MMSE), and executive function tests, eg, trail making test (TMT) A & B time and the executive interview-25 questionnaire (Exit25). Patients aged 27-71 years who had a diagnosis of CADASIL and