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JOURNAL OF THE AMERICAN HEART ASSOCIATION

## Advances in Critical Care and Emergency Medicine

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*Stroke* 2009;40:e298-e300; originally published online Apr 9, 2009;

DOI: 10.1161/STROKEAHA.108.544619

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214  
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ISSN: 1524-4628

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## Advances in Critical Care and Emergency Medicine

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In 2008, there were clinical trial advances in 3 areas that will impact on the way stroke care is practiced in the emergency department and intensive care unit (ICU). These include (1) the positive results of the European Cooperative Acute Stroke Study (ECASS) III trial, extending the time window for intravenous thrombolytic therapy for acute ischemic stroke; (2) the negative results of 2 trials investigating the use of intensive insulin therapy in the ICU; and (3) new data from the Phase 2 Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT), investigating the role of intensive blood pressure (BP) control after intracerebral hemorrhage (ICH).

### ECASS III: Breaking the Time Barrier

Intravenous thrombolysis with alteplase is still the only approved treatment for acute ischemic stroke. However, the time window for applying this therapy, which significantly reduces morbidity but not mortality, up to now has been restricted to 3 hours after symptom onset.<sup>1</sup> Various stroke trials trying to expand this strict time window, selecting patients based on CT or MRI perfusion, and using thrombolytic agents other than recombinant tissue plasminogen activator (rtPA), have up until now failed to prove efficacy regarding clinical end points.<sup>2-5</sup> After a couple of years without any positive stroke trials, ECASS III adds on to the encouraging results of the pooled analyses of the ECASS and National Institute of Neurological Diseases and Stroke trials,<sup>6</sup> now expanding the time window for CT-based treatment of acute ischemic stroke up to 4.5 hours.<sup>7</sup>

The ECASS III trial randomly assigned 821 patients either to receive 0.9 mg rtPA per kilogram body weight or placebo. After ruling out intracranial hemorrhage using CT, thrombolysis was administered between 3 and 4.5 hours (median, 4 hours). The dichotomized primary end point of recovery with no disability after 90 days (modified Rankin scale 0 to 1 versus 2 to 6) was reached significantly more often in the rtPA group (52.4% versus 45.2%; OR, 1.34; 95% CI: 1.02 to 1.76;  $P=0.04$ ). Mortality did not differ significantly between both groups (7.7% in the rtPA group and 8.4% in the placebo group, respectively;  $P=0.68$ ) and there was no difference in the overall rate of serious adverse events.<sup>7</sup> However, the frequency of symptomatic ICH was higher in patients receiving alteplase than placebo (2.4%

versus 0.2%;  $P=0.008$ ). In this context, it needs to be mentioned that despite the expanded time window in ECASS III, the rate of symptomatic intracranial hemorrhage still was comparable to the overall incidence of this most feared thrombolysis-related complication described in Safe Implementation of Thrombolysis in Stroke—MONitoring STudy (SITS-MOST), a large registry of rtPA given within 3 hours of onset.<sup>8</sup> Given this safety aspect, and in light of benefits using intravenous thrombolysis beyond the 3-hour time window, it nonetheless remains essential to keep in mind the time-dependent efficacy of rtPA treatment and to apply this therapy to patients with acute ischemic stroke as soon as possible.

### GLUCONTROL and VISEP: Reconsidering Intensive Glycemic Control

The benefits of using intensive insulin therapy (IIT) to maintain normoglycemia (target serum glucose level 80 to 110 mg/dL) was first demonstrated by Van den Berghe and colleagues in 2001.<sup>9</sup> In this landmark study, mortality was reduced in critically ill surgical patients treated at a single center with continuous insulin infusion compared with conventional fingerstick coverage. The observed mortality reduction was attributed to reductions in the risk of infection, critical illness neuromyopathy, renal failure, blood transfusion requirements, and possibly other unknown factors. In a post hoc analysis of 63 neurological patients included in this study, IIT was also associated with modest but significant reductions in intracranial pressure and seizures.<sup>10</sup> A follow-up study of medical ICU patients conducted by the same group also seemed to indicate that IIT was associated with improved survival, but only in patients with an ICU length of stay of 3 or more days.<sup>11</sup>

With special regard to patients with stroke, however, the UK Glucose Insulin in Stroke Trial (GIST-UK) in 2007 raised doubts regarding the potential clinical benefits of IIT. In this study, glucose-potassium infusion had no effect on outcome compared with placebo, albeit the mean plasma glucose difference between the 2 groups was only 10 mg/dL.<sup>12</sup> To further investigate the role of glycemic control in critically ill patients, 2 prospective, randomized, multicenter studies—the GLUCONTROL and VISEP (Volume Substitution and Insulin Therapy in Severe Sepsis) trials—investigated

Received and accepted December 4, 2008.

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(*Stroke*. 2009;40:e298-e300.)

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*Stroke* is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.108.544619

whether IIT improves the outcome of general critical care patients or impacts on mortality rate or the frequency of organ failure in severe sepsis patients, respectively.<sup>13,14</sup> Both trials compared 2 insulin infusion regimens with one group being intensively treated with insulin to maintain serum glucose levels between 80 to 110 mg/dL and another group whose glucose levels were maintained between 140 and 180 mg/dL. Both the GLUCONTROL and VISEP study were stopped early for safety reasons.<sup>13,14</sup> Whereas in each case the overall clinical outcome and mortality rate did not significantly differ between both groups, the incidence of severe hypoglycemic episodes and adverse events in the IIT groups was higher in the ITT-treated patients. A more recent single-center study of ICU patients has since replicated these findings, casting further doubt on the balance of risk versus benefit with strict glycemic control.<sup>15</sup> The situation gets even more interesting in light of 2 recent articles indicating that normoglycemic control increases the risk of critical brain tissue hypoglycemia and tissue metabolic crisis in comatose brain-injured patients monitored with cerebral microdialysis.<sup>16,17</sup>

With more questions than answers regarding ITT these days, it is clear that much more research in this area is needed. Ideally, the best approach in the ICU would be to maintain normoglycemia with an insulin infusion protocol that minimizes the risk of hypoglycemia. Still, for the practicing stroke specialist, it should be remembered that there is compelling evidence to prevent hyperglycemia in patients with acute ischemic stroke treated with thrombolytic therapy. Uncontrolled hyperglycemia in this setting is associated with reduced rates of vessel recanalization<sup>18</sup> and, even more importantly, a greatly increased risk of hemorrhagic transformation.<sup>19,20</sup>

### INTERACT: Control of Blood Pressure After ICH

Over the past decade, large clinical trials of surgical hematoma evacuation and ultraearly hemostatic therapy have failed to consistently demonstrate improved outcomes.<sup>21,22</sup> Thus, effective medical treatments for ICH are long overdue. Severe hypertension is common during the acute phase of ICH and has been linked to poor outcome,<sup>23,24</sup> but little is known about the relative risks and benefits of reducing BP aggressively during the acute phase of bleeding. Theoretically, control of hypertension might reduce active bleeding and ICH volume growth within the first 6 hours after hemorrhage onset and minimize tissue edema and intracranial hypertension in the days that follow.

The Phase II INTERACT enrolled 404 patients with ICH with elevated systolic BP (150 to 220 mm Hg) within 6 hours of onset.<sup>25</sup> Patients were randomly assigned to intensive BP reduction (target systolic BP, 140 mm Hg) or standard guideline-based management of BP (target systolic BP, 180 mm Hg) with intravenous agents, including diuretics and calcium channel blockers. Treatment was started on average 4 hours after onset; 1 hour later mean systolic BP was 153 mm Hg in the intensive treatment group and 167 mm Hg in the guideline group ( $P < 0.0001$ ). Although mean proportional ICH volume growth at 24 hours was 36% in the guideline group and 14% in the intensive treatment group,

after adjustment for initial ICH volume and time from onset to CT, this difference just missed statistical significance ( $P = 0.06$ ). Viewed another way, the absolute difference in ICH volume growth between groups was only 1.7 mL ( $P = 0.13$ ). In comparison, the absolute reduction in ICH volume growth in the negative Phase III FAST (Factor VII for Acute Hemorrhagic Stroke Trial) trial of recombinant activated Factor VII for ICH was 3.8 mL.<sup>22</sup> Intensive BP reduction in INTERACT did not influence the risk of adverse events or secondary clinical outcomes at 90 days.

Current American Stroke Association guidelines and a recently convened National Institutes of Health expert panel on the management of ICH have emphasized the need for definitive studies of BP management.<sup>26,27</sup> The INTERACT study is important because it is one of the first to shed light on this “evidence-free” zone and demonstrates the safety and feasibility of aggressive BP reduction in the emergency department targeted at a systolic BP of 140 mm Hg. It remains to be seen, however, whether intensive BP control can definitively reduce ICH volume growth and improve outcome as a solo intervention. Earlier treatment with hemostatic therapy,<sup>28</sup> in combination with intensive BP control, would seem to be the most promising investigational strategy for substantially reducing hematoma expansion in the acute phase of ICH.

### Disclosures

S.A.M. receives research support, consulting fees, and speaking honoraria from Novo Nordisk A/S and Medivance, Inc; speaking honoraria and consulting fees from The Medicines Company, Inc; and speaking honoraria from EKR Therapeutics, Inc.

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KEY WORDS: advances ■ critical care ■ emergency medicine