The emergency room is the front line in the battle against stroke. In 2007 the results of 2 phase III international stroke trials were announced: DIAS-2 evaluated IV recombinant tissue plasminogen activator (rtPA) within an expanded time window based on the demonstration of MR perfusion-diffusion mismatch, and FAST was designed to confirm the clinical benefits of early hemostatic therapy with recombinant activated factor VII (rFVIIa) for intracerebral hemorrhage (ICH). These trials promised to usher in a new era of therapy for thousands of acute stroke victims in our emergency departments. Unfortunately, both trials were negative. On the brighter side, however, a meta-analysis of 3 European hemicraniectomy trials for middle cerebral artery (MCA) infarction showed a powerful mortality reduction. These studies have established hemicraniectomy with duroplasty as the treatment of choice for younger patients (<60 years) admitted to intensive care with medically refractory edema and intracranial pressure related to MCA infarction.

Hemostatic Therapy for ICH: The FAST Trial

ICH is widely recognized as the deadliest and least treatable form of stroke. Thus, it was with great anticipation that the results of the FAST trial were announced at the European Stroke Congress in Glasgow in the spring of 2007. FAST was designed to confirm the strikingly positive results of an earlier phase IIIB trial investigating the effects of rFVIIa on hematoma expansion in the acute phase of ICH. In addition to an approximate 50% reduction in ICH volume growth, 3 doses of rFVIIa (40, 80, and 160 μg/kg) were collectively associated with a statistically significant 38% mortality reduction, as well as improved functional outcomes according to the modified Rankin scale (mRS).

In FAST, the experiment was repeated with the exact same inclusion and exclusion criteria (no upper limit on baseline ICH volume), time window (up to 4 hours), and clinical outcome measure (the frequency of death or severe disability [mRS 5 or 6] at day 90). The doses studied were 20 and 80 μg/kg. But this time, the beneficial effects of rFVIIa treatment on clinical outcome were not confirmed. There was essentially no effect on mortality, or on the spectrum of mRS outcomes. This was the case despite the fact that rFVIIa had exactly the same safety profile (a 5% risk of an arterial thromboembolic event) and a slightly better hemostatic effect.

What happened? The conflicting findings of the phase IIIB and III trials at first seem difficult to understand, but on closer inspection, some explanations become apparent. The most striking discrepancy is the remarkably improved 3-month outcomes of the 268 placebo patients enrolled in FAST (24% mRS 5 or 6) compared with the 96 placebo patients in the phase IIIB study (45% mRS 5 or 6). It seems most likely that the phase IIIB placebo group did extraordinarily poorly, and the FAST placebo group fared surprisingly well, both due to chance effects. Supporting this concept is the fact that there were potentially important randomization imbalances in FAST, particularly regarding the presence of intraventricular hemorrhage at baseline (29% in placebo versus 41% in the 80 μg/kg group). Another important source of “noise”—death or severe disability unrelated to the bleed itself—were late-occurring medical complications such as nosocomial infections, renal failure, and cardiac arrhythmias. These events were much more common in very elderly patients and tended to “dilute” the signal the study was designed to measure: whether a treatment that reduces ICH lesion volume can translate into improved survival with a good outcome.

Both FAST and the earlier phase IIIB study indicate that little active bleeding occurs between the third and fourth hours after ICH onset. Treatment with rFVIIa after 3 hours thus exposes patients to the 5% risk of an arterial thromboembolic event, without much potential for benefit. Perhaps the most important lesson learned from FAST is that to effectively improve outcome, hemostatic therapy must be targeted to patients who are actively bleeding. Reducing onset-to-needle time to 2.5 hours or less will be necessary in future studies evaluating rFVIIa for ICH. Among patients in FAST ≥70 years of age, with baseline ICH volumes ≤60 mL, IVH volumes ≤5 mL, and an onset-to-needle interval ≤150 minutes, the adjusted odds ratio for poor outcome at 90 days with rFVIIa was 0.28 (95% CI, 0.08 to 1.06) compared with placebo. Selection of patients based on contrast extravasation into the clot after CT angiography (“spot sign”) is another promising approach currently being evaluated. In our view, until more data are available off-label use of rFVIIa should be restricted to the emergency reversal of warfarin anticoagulation in patients with acute intracranial bleeding in
order to expedite a potentially life-saving neurosurgical procedure.

**MR Perfusion Diffusion Mismatch: DIAS-2**
The rigid and narrow time-window of 3 hours for thrombolytic therapy is arguably the single most important factor that has hampered the wider use of this therapy over the past decade. Expanding the time-window for thrombolysis is among the most important and extensively studied topics in current research on the treatment of acute ischemic stroke. Based on several case series and small trials of multiparametric MRI techniques using the “perfusion-diffusion mismatch concept,” clinical practice to select patients for thrombolysis in an extended time-window has been incorporated in many high-volume stroke centers around the world.

Two large observational studies using stroke MRI in an extended time-window have been published, thus providing at least level II evidence supporting this therapeutic paradigm. Thomalla et al compared outcome and symptomatic bleeding complications of intravenous rtPA within 6 hours in MRI-selected patients with the pooled data of the large stroke rtPA trials. Köhrmann et al compared patients who were treated with rtPA based on CT findings within 3 hours to patients who received MRI-based treatment within, or later than, 3 hours. In both studies safety and clinical outcome of patients treated beyond 3 hours based on tissue at risk as defined by MRI were comparable to the outcomes of patients treated within 3 hours.

DEFUSE recruited patients treated within 3 to 6 hours after symptom onset. An MRI was obtained immediately before and after rtPA. Only patients with a mismatch benefited from thrombolysis and early reperfusion, whereas others did not. This study has helped establish the concept that MRI perfusion-diffusion mismatch can identify patients that are likely to benefit from late (3 to 6 hours) reperfusion, as well as those who are unlikely to benefit or may be harmed.

The DIAS and DEDAS trials used desmoteplase within a time window of 3 to 9 hours applying the MRI-mismatch selection process. Desmoteplase is a highly fibrin specific and non-neurotoxic thrombolytic agent derived from vampire bat saliva. Both were phase II studies using a dose-escalation design. In both studies, 125 µg/kg was found to be the optimal dose of desmoteplase; higher doses caused excessive intracranial hemorrhage in DIAS. At this optimal dose, desmoteplase given between 3 to 9 hours in patients with MRI tissue at risk had higher reperfusion rates and better clinical outcomes than placebo-treated patients.

It was thus with great anticipation that the phase III DIAS-2 results were announced in the spring of 2007 at the European Stroke Conference.

The DIAS-2 study compared 90 and 125 µg/kg of desmoteplase to placebo in patients with documented CT or MRI mismatch between 3 to 9 hours. Surprisingly enough, the DIAS-2 trial failed to show efficacy, but safety in terms of excess bleeding was not a problem. Mortality was actually increased with the 125 µg/kg dose versus both placebo and the 90 µg/kg dose, although the excess deaths occurred late after treatment and were predominantly non-neurological, according to the investigators. Until now, it is not well understood what the explanation for the negative result is. Because the trial did not include mandatory information on occlusion site and recanalization, it can be speculated that patients with already open vessels might have hampered the clinical and neuroradiological end points. Another issue could be the difference of patients enrolled on a CT-perfusion basis, and those treated according to MRI criteria. A possible lesson from this failed trial is to treat patients after 3 hours only with a proven large proximal vessel occlusion and a neurological deficit with an National Institutes of Health Stroke Scale >8. Even though the result of the DIAS-2 was disappointing, it is another step toward more knowledge to select patients who can benefit from recanalization therapies beyond 3 hours. We are now awaiting the results of another placebo controlled trial, the EPITHET study, to further clarify this important issue.

**Hemicraniectomy: DESTINY, DECIMAL, and HAMLET**
Management of brain edema related to MCA territory infarction is a common indication for admission to a neurocritical care unit. Decompressive hemicraniectomy and duroplasty is intended to prevent the death spiral after MCA infarction by normalizing intracranial pressure, restoring compromised flow in adjacent vascular territories, and restoring the midline position of the brain stem and diecephalon. Despite evidence from nonrandomized studies that hemicraniectomy can improve survival, concerns have always existed about the quality of survival in these patients, making this procedure one of the most controversial in stroke care.

In the spring of 2007 Vahedi et al reported a groundbreaking pooled analysis of 3 European hemicraniectomy trials: DESTINY, DECIMAL, and HAMLET. All 3 of these studies limited enrollment to patients ≥60 years of age, and the timing of surgery to <48 hours after stroke onset. A total of 93 patients were randomized to surgical or medical therapy and evaluated with the mRS at 1 year. Hemicraniectomy more than doubled the chances of survival, from 29% to 78%. This staggering absolute risk reduction of 49% was highly significant and translates into a number needed to treat of two to avoid 1 fatality. More importantly, hemicraniectomy did not increase the risk of complete dependency. Exactly 2 patients in the surgical and medical groups (approximately 5%) were bedbound and severely disabled (mRS level of 5) at 1 year. Viewed another way, for every 10 hemicraniectomies performed for MCA infarction, 5 patients escaped death, and at 1 year one of these patients had just mild disability (mRS 2), one had moderate disability (mRS 3), and three had moderate-to-severe disability (ie, unable to walk independently, mRS 4). This information may be helpful for explaining the anticipated outcome of this procedure to families.

Although not without flaws (primarily its small size and lack of caregiver blinding), the meta-analysis by Vahedi et al indicates that hemicraniectomy in patients <60 years is a life-saving procedure that can produce reasonable functional outcomes. However, as clinicians increasingly incorporate hemicraniectomy into clinical practice, practical questions will arise. What is the most appropriate trigger and timing for
performing the procedure? The pooled analysis by Vahedi et al found no additional benefit with surgery performed within 24 hours compared with surgery performed later. Some centers have adopted the development of >7 mm of septal shift in addition to lethargy as an appropriate and easy-to-identify trigger. Should patients with dominant hemisphere infarction undergo the procedure? The answer is yes: functional outcomes in the meta-analysis were similar regardless of laterality. Finally, given the absence of data in older patients, when should hemicraniectomy be offered to patients over 60? In a systematic review of published hemicraniectomy cases, younger age (in this case dichotomized at 50 years) was the only preoperative clinical determinant of survival with good functional outcome. Older patients who survive hemicraniectomy cannot be expected to have functional outcomes that are as good as younger patients. Until more data are available, clinicians will need to struggle with where to “draw the line” in terms of offering hemicraniectomy as a treatment option for older patients.

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References


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