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## Advances in Emerging Therapies

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Historically, stroke has proven to be a condition poorly amenable to treatment, and the last year delivered its share of neutral results in this regard. However, other studies suggested promising areas for pursuit while a couple grabbed the headlines and will modify clinical practice.

### Thrombolysis

We can justifiably emphasize the findings of the third European Cooperative Acute Stroke Study (ECASS-3), which has recently confirmed the use of thrombolytic therapy up to 4.5 hours after onset of ischemic stroke.<sup>1</sup> The reality is that alteplase was already a safe and highly effective treatment before the results of ECASS-3 became known. However, a minority allowed their uncertainty over safety and doubts raised by individually neutral trials to restrict implementation of this potent therapy. The latest result broadens the range of patients who may benefit but it has implications beyond these narrow confines. Even after accounting for the expected low rate of symptomatic bleeding—just 2% excess over placebo—alteplase treatment delivered a 10% absolute increase in proportion of patients attaining excellent outcome, indicating 3 valuable lessons. First, any residual doubts over the safety or efficacy of intravenous alteplase early after stroke have been annulled. Second, the challenging time window for treatment can be relaxed, provided this is not at the expense of slower reaction by services. Third, there is evidently scope for further extension of treatment and enhancement of alteplase's action that begs continued research. We need to test extended patient selection, perhaps via imaging strategies. We must also assess whether we can enhance the extent and rapidity of reperfusion. This may involve incorporating ancillary measures such as antithrombotic therapy and blood pressure manipulation.

One of our challenges is to divorce enhancement of reperfusion from exacerbation of serious bleeding risk. Both better patient selection and careful pharmacological profiling are required. By harnessing our very active clinical services to contribute actively to research, we could make rapid strides. The SITS register's examination of treatment 3 to 4.5 hours after stroke onset illustrates that over 12 000 patients were treated 'within label' in participating centers while ECASS-III was enrolling.<sup>2</sup>

The EPITHET study<sup>3</sup> used perfusion neuroimaging to identify patients expected to benefit from thrombolytic treat-

ment beyond standard treatment windows. In patients with perfusion-/diffusion-weighted imaging mismatch, alteplase increased reperfusion and was associated with enhanced functional outcome. Unfortunately, EPITHET lacked power to confirm whether selection by imaging beyond the licensed time window is ready to be introduced. The ECASS-3 result and EPITHET together should convince us to redouble our efforts to test delayed thrombolysis in carefully selected patients who present too late for standard care.

We know that alteplase achieves reperfusion neither immediately nor universally. While the evidence base for alteplase expands, encouraging data for another thrombolytic, tenecteplase, was presented at the International Stroke Conference (ISC). In their pilot study, Molina et al<sup>4</sup> demonstrated better rates of recanalization and functional outcome at 3 months, against a trend toward increased hemorrhage.

Ultrasound-assisted thrombolysis may improve recanalization rates, though increased bleeding has also been observed. Eggers et al,<sup>5</sup> using a transcranial ultrasound delivery device, confirmed increased recanalization at the expense of a trend to increased hemorrhage, leading to premature discontinuation of their study. Ultrasound-assisted lysis merits more robust safety evaluation, in which dose and delivery modality are thoroughly evaluated. We must not let regulatory laxity over evaluation of devices diminish our rigorous appraisal of their potential. We await with interest the results of studies such as TRUST, evaluating the safety and efficacy of 60 minutes' continuous insonation of the occluded middle cerebral artery in patients with ischemic stroke given intravenous alteplase.

We can refer to extensive observational data implying efficacy of intra-arterial thrombolysis, but we lack comparative studies against intravenous (IV) administration. SYNTHESIS EXP is a phase III study being designed to assess whether local intra-arterial tissue plasminogen activator (tPA), as compared to IV tPA, can increase survival free from disability.

Recovery after thrombolysis requires successful restoration and maintenance of blood flow. Intuitively, antiplatelet therapy should help prevent reocclusion. Current stroke guidelines reflect concern that the risk of symptomatic bleeding may be unacceptable if antithrombotic therapy is given alongside alteplase. Such caution may be misplaced. Uyttenboogart et al<sup>6</sup> have published prospective observational data

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assessing the impact of antiplatelet therapy in patients undergoing thrombolysis. They confirmed an increased risk of symptomatic intracranial hemorrhage among patients already established on antiplatelet therapy, but report that the net effect on functional outcome remains favorable. Such studies reinforce the importance of measuring robust outcomes in acute stroke, using tools that combine risk and benefit in a unified measure, such as the modified Rankin Scale. ARTIS, a phase III trial to confirm whether the addition of aspirin to standard rt-PA thrombolysis offers additional benefit, is ongoing.

Alternative antiplatelet agents suffered a setback. The discontinuation of the AbESTT-II study due to excess bleeding has raised concern about glycoprotein IIb/IIIa inhibitors in acute stroke.<sup>7</sup> Perhaps coronary doses do not translate to the brain: there is no such thing as a safe drug, only one used at the optimum dose. Other agents in this class continue to be evaluated. Encouraging safety results were observed in the CLEAR study for eptifibatid, used in combination with alteplase in the acute setting.<sup>8</sup>

Old trials based on a different standard of care can unduly impede progress. We know little about heparin use in modern circumstances. Perhaps it is time to revisit the role of antithrombotics in acute stroke, at least post-thrombolysis.

### Antiplatelets

Results of the largest study last year, PROFESS,<sup>9</sup> had been eagerly anticipated to show the extent of advantage conferred by the combination of aspirin with dipyridamole over clopidogrel monotherapy. To the surprise of many, PROFESS demonstrated that the 2 strategies are equal. Far from representing a “negative” study, this is important information that will impact on our practice, because dipyridamole is not universally tolerated. The interpretation has been debated widely, but perhaps the crucial message is that although a simple aspirin remains cheap and universally available, it is not a panacea.

### Antithrombotics

In prevention, the search for alternatives to warfarin continues because of its inherent bleeding risk and monitoring requirements.

Full results of the Amadeus<sup>10</sup> study were published this year. Idraparinux was associated with significantly greater bleeding complications than warfarin. Its safety profile does not presently commend it as a viable alternative to warfarin.

Direct thrombin inhibitors (DTI) have also been compromised by safety concerns. Further analysis of the SPORTIF III and V trials<sup>11</sup> among elderly patients with atrial fibrillation demonstrated similar efficacy in stroke reduction by the DTI ximelagatran as with warfarin. Bleeding complications were fewer in the DTI group despite more intensive international normalized ratio monitoring for the warfarin group than we often see in clinical practice. However, an excess of liver function derangement was again observed with ximelagatran. Though ximelagatran itself seems doomed, this analysis lends cautious optimism for DTIs as a general alternative in patients requiring anticoagulation but in whom warfarin is deemed inappropriate. We await results of the RE-LY study,

which evaluated dabigatran in a similar setting. We also look forward to the Argatroban TPA Stroke Study, which is evaluating the role of a DTI in the hyperacute setting to augment thrombolytic therapy.

### Other Avenues

Hyperglycemia is associated with adverse outcome and so induction of normoglycemia as part of acute management carries face validity. The disappointing results of intervention for mildly elevated sugars in GIST-UK may relate to the choice of glucose-potassium-insulin infusion as the means of lowering blood sugar and/or to statistical underpowering. Bruno et al<sup>12</sup> instead used a continuous intravenous insulin infusion according to sliding scale as a means for correcting hyperglycemia in the THIS study. Greater reductions in glucose were observed using this approach with no apparent excess in adverse events. Their study was not powered to look at overall outcome but demonstrated nonsignificant improvements in functional outcome in the more aggressively treated group.

A pilot study of granulocyte-colony stimulating factor (the AXIS study<sup>13</sup>) was presented at the ISC. Based on promising results in animal models this study sought primarily to evaluate the safety of granulocyte-colony stimulating factor in humans. Apparent demonstration of safety in the small study population was supplemented with a trend toward improvement in functional outcome in the treatment group. This intriguing finding merits further evaluation.

Yusuyaki presented case-controlled data at the ISC suggesting modest improvements in clinical outcomes with the free radical scavenger edaravone,<sup>14</sup> a drug with some parallels to NXY-059 used in the SAINT program but licensed in Japan. The ECCT-HIS study will prospectively evaluate edaravone along with citicoline, a second potential neuroprotectant agent which is also under investigation in the ICTUS trial.

A study with erythropoietin (EPO) as neuroprotectant recently announced a negative result, possibly due to increased risk of mortality in a subgroup. Whether the drug is salvageable has yet to be determined. The REGENESIS study, evaluating EPO and hCG in combination may provide further answers, if an FDA hold on recruitment pending details of the EPO study is lifted. Clinical work with a carbamylated derivative of erythropoietin, CEPO, which is apparently devoid of hematologic effects, was announced at the 2008 Thrombolysis and Acute Stroke Therapy conference in Budapest.

Finally, we must not forget that devices to assist cooling remain under development, and that hypothermia is a potentially potent natural neuroprotectant.

### Summary

At least 2 large clinical trials published over the last 12 months will modify practice, in acute treatment and secondary prevention respectively. We have exciting support for thrombolysis and a stimulus to expand our efforts to restore perfusion in a wider range of patients. Elsewhere we see encouragement that improvements in therapy are emerging, and hope to see these flourish over the coming year.

## Disclosures

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