Letters to the Editor 2431

Main Uncertainties for Intravenous Thrombolysis With rtPA up to 6 Hours in Patients With Acute Ischemic Stroke

1. Estimations of effect in the individual trials
2. Effect of rtPA on death from all causes
3. Effect on functional outcome, heterogeneity, and imprecise estimates
4. Effect in older people
5. Safety in older people
6. Clinical selection criteria
7. CT features reliably predicting response to thrombolysis
8. Potentially maximal, or individual, time window between onset of stroke and treatment
9. Patients already on antithrombotic therapy at stroke onset
10. Implication of the type of ischemic stroke
to criteria derived from completed randomized trials. A quality register gives the means to identify rare side effects and to monitor the uptake of a new treatment. In theory, it may be of interest to compare findings in a quality register to findings in earlier trials (historical controls). However, such comparisons have very limited scientific value because the lack of randomization will inevitably introduce bias. By necessity there will be a long delay between the trials and the analysis of the quality register. Hence, there is no way of adjusting for case mix or for the many immeasurable changes in treatment that may have occurred over time. For example, today a much larger proportion of patients are already on antiplatelet treatment, and refinement of diagnostic tools may influence the type of patients who are entered in the register. An example of the effect of changes over time is the difference between the placebo-treated patients entered in ECASS I and ECASS II where, in the latter trial, the course of disease was much better despite similar inclusion criteria.

Despite the positive effect of thrombolysis shown in the systematic reviews, there are prevailing, definite, and important uncertainties (Table). We believe that these questions can only be answered validly and reliably by large RCTs, and not by observational studies and quality registers.

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Quantitative Ultrasonographic Evaluation of Cerebral Perfusion in Acute Stroke Is Possible

To the Editor:

With much delight we have read in the issues 2, 5, and 7 of *Stroke* that ultrasonic perfusion imaging of the brain achieves more and more recognition in the community. In these very well conducted studies, the authors have proven the ability of the method of predicting localization and size of final infarction in the acute state. Even though of different technical background, there are now 5 studies with a considerable cohort of about 120 patients altogether suffering from acute stroke examined by ultrasonic perfusion imaging. With parametric imaging, the diagnosis becomes quick and easy, clinical outcome can be forecasted, and a microbubble-destructive approach decreases time of examination considerably. However, two main drawbacks of the different methods remain: only 1 hemisphere is examined so that quantitative comparison with healthy referential tissue is only possible with a second (contralateral) examination; the evaluation of the microbubble kinetic is performed in a way that quantification is only possible in a "perfusion yes/no" manner.

Since visualization of perfusion deficits has obviously improved so much since the early days, we propose that future studies should gain for a semiquantitative bilateral examination with the aim of differentiating ischemia and hyperperfusion in the acute state. A bilateral examination (having both hemispheres in the field of view) using the bolus kinetic yields stable parameters throughout the field of view, where regions of one hemisphere can be compared with the same regions of the other hemisphere. Interindividual ranges of the resulting parameters are considerable due to various cardiovascular reasons. However, intraindividual ranges of eg, the time-to-peak intensity (TPI) are very small. In 20 healthy volunteers, the mean quartile deviation of TPI values in individual 14 regions throughout both hemispheres was 0.68 seconds, and there was no case in which any TPI exceeded the individual mean for more than 2 seconds.

Initial TPI parametric image with a visible TPI delay in the reddish and white circled area and no detectable perfusion kinetic in the pinkish and black circled area (white arrow: frontal ventricular horns; black star: 3rd ventricle, midline; black arrow: posterior ventricular horn; dotted lines: near field and side field artifacts); follow up CCT 5 days after clinical successful thrombolysis (NIHSS from 13 to 5) with an infarction in the area corresponding to initial black circled area in ultrasonic perfusion imaging; Phase Inversion Harmonic Imaging, bolus kinetic, Sonovue 2.5 mL, fitted model function, field of view 150 mm.
The Need to Recognize the Difference Between a Quality Register and a Randomized Controlled Trial

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