Response to Letter by Furlan

In response to the thought-provoking commentary by Anthony J. Furlan, we would like to place the issue in even clearer perspective. When deciding to conduct a randomized control trial, the main driver is to provide evidence of sufficient quality to change clinical practice. Inherent in this statement is the assumption that the current evidence is inadequate. Is the evidence for reperfusion in the 3- to 6-hour time window in this category? The resounding answer must be “yes,” particularly when the type of reperfusion strategy is contemplated. For example, if reperfusion devices are considered, no Phase III evidence exists. For intra-arterial thrombolysis, evidence for one randomized, controlled trial using prourokinase exists.1 Interestingly, this was not considered to be adequate evidence at the time by either the Food and Drug Administration or the Prolyse in Acute Cerebral Thromboembolism (PROACT) investigators. PROACT 2 was planned but did not proceed because of sponsorship difficulties. For intravenous tissue plasminogen activator, the evidence is now very adequate up to 4.5 hours, although it could be argued that this excludes those aged >80 years, nondiabetics, and other groups.2

The current controversy has some parallel with the carotid endarterectomy debates of the 1980s. At that time, an unproven intervention (endarterectomy) with only a modest amount of evidence was being promulgated as the management of choice by many practitioners, mainly surgeons. The enthusiastic user group (vascular surgeons) has now been replaced in the current argument by interventionalists. How we applauded the investigators with the courage to insist on carefully conducted randomized control trials with placebo arms to establish not only if the intervention was effective, but under what circumstances and with what risk–benefit ratio.

As clinicians, we have responsibilities to our patients to advance medical knowledge using appropriate research tools such as the randomized control trial so that they may ultimately benefit. Should we deviate from this principle because of assumed rather than proven knowledge, we are regressing to practices only too common ≥30 years ago.

Furlan does make a very important point about the design of trials moving forward in an attempt to extend the time window beyond that used in current practice. We support his view that homogenous clinical groups are now required3; hence, our use of penumbral selection techniques in our soon-to-be-launched EXTEND (Extending the time for Thrombolysis in Emergency Neurological Deficits) trial.4,5 Here, we will randomize patients based on MR penumbral mismatch beyond 3 hours (or 4.5 hours, depending on local practice). This will include those who awake from sleep up to a time window of 9 hours. The vanguard phase will be conducted in Australia, Asia, and Europe with a sample size of 100 patients with the expectation that we will expand this to a sample size of approximately 400 patients as partners join from other continents. Only with this trial and International Stroke Trial (IST)3b (0- to 6-hour time window) completed do we believe that adequate randomized control trial evidence will be in place to change clinical practice.

Disclosures

None.

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