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Reading the entrails of a decade of stroke trials: how do we get it right next time?

The majority of drug treatments developed for treatment of acute stroke over the past decade have failed, the notable exception being alteplase for acute ischaemic stroke. Recent phase II trial successes signal potential for recombinant activated factor VII for primary intracerebral haemorrhage, desmoteplase for ischaemic stroke, and the nitron free radical spin trap agent NXY-059, the latter being the first neuroprotectant to show evidence of efficacy.

The reasons for the many trial failures are debated. They almost certainly include poor understanding of animal model systems by clinical trialists, inadequate preclinical testing, inefficacy of drugs, dose-limiting drug toxicity, and incomplete characterisation of pharmacokinetics. Clinical trial design has been slow to evolve, with most trials afflicted by inadequate sample size due to unrealistic treatment effect sizes, long time windows, heterogeneity of study populations, and poor characterisation of trial end-points. The failure of MATCH and other trials of antithrombotic therapy for secondary prevention is probably attributable to a failure to appreciate the heterogeneity of stroke pathophysiology and mechanisms. The successful acute trials are notable for several factors, notably very short onset-to-treatment times, but also homogenisation of trial populations by use of brain imaging and the incorporation of imaging biomarkers as outcome surrogates in "proof of concept" trials.

Insights from previous clinical trial programmes, both successful and unsuccessful, suggest approaches that will enhance future clinical trial design. Changes brought about by the implementation of routine IV thrombolysis, and increasing availability of advanced brain imaging techniques, provide the substrate for larger and better designed clinical trials in future. This applies both to acute stroke trials, and to secondary prevention trials.