# A POOLED ANALYSIS IDENTIFIES THE POTENTIAL TO IMPROVE UPON INTRAVENOUS rt-PA

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## Abstract

**Introduction**: Intravenous thrombolysis (IVT) remains the most effective therapy for ischemic stroke. While non-randomized series suggested better outcomes for endovascular and other approaches, randomized clinical trials (RCTs) were usually negative. Because baseline imbalances affect all but the largest trials, we developed analytical techniques that obviate the need for statistical adjustment of these imbalances, to better identify efficacious therapies and applied them here to assess approaches to improve upon IVT.
**Methods**: We generated pooled outcome (mRS 0-1/0-2) models from the thrombolytic arms of all RCTs, with the novel feature of multi-dimensional statistical intervals to assess each study's outcomes at its own baseline median NIHSS and age against the model. We analyzed IVT alternatives, add-on therapies and recent endovascular/thrombectomy trials.
**Results**: Non-linear functions from 18 IVT RCT arms representing 2767 subjects resulted in excellent fits ($r^2 \geq .64$). Eighteen studies were analyzed. TUCSON (3 hour IVT/ultrasound with microspheres), CLOTBUST (3 hour IVT/ultrasound) and SYNTHESIS (3 hour IA rt-PA) Tenecteplase (3.1 average time window, image-guided) and Cerebrolysin (3 hour window) showed significant improvement. No thrombectomy or longer window trials showed benefit.
**Interpretation**: Adjunctive treatments or IA rt-PA mostly with a 3 hour treatment window appear to be the most promising approaches, indicating that, analogous to the cardiac literature, there remains little evidence that the window can be extended other than by tPA or newer IV thrombolytics.

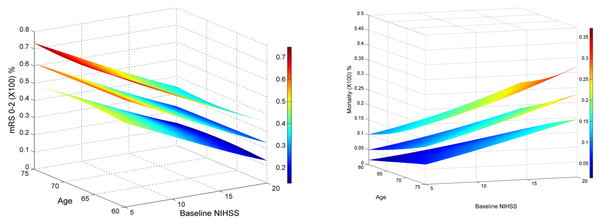
## Background

Translating pre-clinical neuroprotectant discoveries into an approved therapy has been for the most part a failure with multiple negative Phase 3 trials after apparently positive earlier Phases. There are many potential reasons for this, but we contend that traditional clinical trial analysis is not appropriate for small trials in heterogeneous diseases like stroke. Inevitable imbalances in baseline factors influence outcomes through differences in natural history. Most trial analysis employs some version of multivariate adjustments, such as CMH test or others to correct for this. However, most statistically adjusted early Phase neuroprotectant RCTs have failed in Phase 3 and no apparent positive subgroup has subsequently been confirmed in a larger Phase 3 trial. A possible reason these correction methods fail is that the distribution of baseline factors is complex, non-linear and often not overlapping between arms while most correction methods require linear and overlapping distributions.

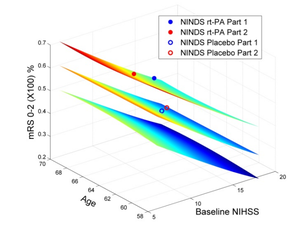
A second reason that early trials appear more positive than they ultimately turn out to be is that there is focus on a positive statistic in an individual study without considering how *representative that study is among the disease population as a whole.* A neglected purpose of statistics is to assess how representative a sample is to the population at large. Random variation in the characteristics of the subjects recruited will influence every study and its reproducibility in a larger sample. Publication bias and funding agencies favor a positive result even if the sample is small.

We elected to address this issue by avoiding the need for statistical correction and instead generating a pooled control sample from the placebo arm of large randomized clinical trials (RCTs) with which we can compare an individual study at its own baseline characteristics without the need for any statistical adjustment. The novel feature is the generation of multidimensional statistical intervals that incorporate variation into a predictive model. We call this model **pPREDICTS©** (pooled Placebo REsponse DICtates Treatment Success; Mandava and Kent, Stroke 2009) and it is based on 30+ control arms of Stroke RCTs representing more than 9000 subjects. With this model, we can compare treatment arms at a range of baseline variables that influence outcome. Studies can be assessed for how representative their control arms are compared to a larger sample.

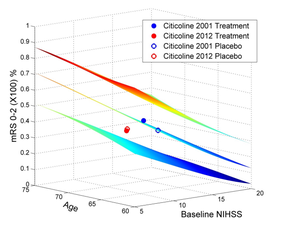
The pPREDICTS© model can be seen in Figure 1 showing the relationship between baseline NIHSS, age and good functional outcome (mRS 0-2) and mortality. We illustrate the use of the model in showing how Part 1 and Part 2 of the NINDS trial would both show greater improvement on functional outcome than the pooled sample (above the top surface, p<.05 improvement) as well as illustrating the imbalances in the controversial Part 2. As an example of its use as a tool to "predict" whether an early phase trial may be positive, we show the 2002 Citicoline results compared to the Phase 3 ICTUS 2012 trial results. While there was a higher percentage of subjects in the treatment arm of the 2001 trial that improved, you can see from the model that this is entirely based on less severe baseline parameters as both results lie on the pooled function. The subsequent Phase 3 trial shows less imbalance, as expected from a larger study, somewhat worse overall outcomes compared to the predicted model, and no evidence of benefit. Note that this result contradicts the accompanying editorial that suggests lack of benefit is due to improved overall outcomes since the original trial.




pPREDICTS© good functional outcome (mRS0-2; $r^2$ = .81) and mortality ($r^2$ = .69) with respect to baseline NIHSS and age. The pooled model based on the control arms of >30 RCTs is the middle surface surrounded by prediction intervals at the p<.05 level. Studies whose outcomes are above the upper surface on mRS 0-2 function would be considered to have improved outcome. Similarly, outcomes below the lower surface on mortality would be expected to have worsened outcome .




Part 1 and 2 of NINDS treatment and control arms. Both control arms were near the middle surface, indicating the results are representative of a pooled control sample. Both tPA arms are above the 95% interval, indicating they are significantly better at the p=.05 level. The different location of the control and tPA arms of Part 2 illustrate the baseline imbalance. Note that the control arm outcomes are comparable to the pooled model despite being based on trials conducted in the following 18 years.




Treatment and control arms of citicoline trial completed in 2001 and ICTUS trial completed in 2012. There was a higher proportion of treated subjects in the initial trial that achieved an mRS 0-2, but it can be appreciated that this was because of less severe baseline NIHSS rather than a treatment effect since both arms lie on the control surface. The follow up larger ICTUS trial had minimal imbalance between treatment and control arms, but both lie between the control surface and the -95% interval indicating overall worse outcomes than in 2001, and no signal of treatment effect. In essence, pPREDICTS of the 2001 data would have predicted a negative follow up result.

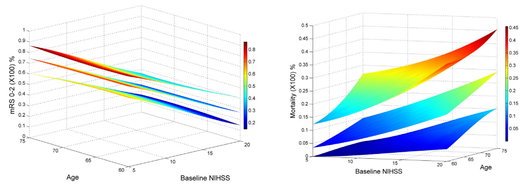
## Objective

There have been numerous attempts to improve upon rt-PA, including adjunctive medications and other therapeutics, endovascular intervention if patient did not improve after IV rt-PA, newer thrombolytics and attempts to extend the time windows beyond 3 hours. **The Objective of this study was to generate a pooled outcome model derived from the intravenous tPA arms of RCTs in order to assess whether there is additional benefit from add-on, adjunctive and newer agents to standard IV tPA**.

## Materials & Methods

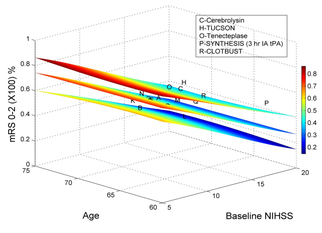
For this study, we repeated the same pPREDICTS method but this time use the tPA arms of RCTs and attempted to generate a function comparing outcomes to baseline NIHSS and age. We employed studies with a time window 3-6 hours. For mRS 0-2, we found 16 trials, representing 2584 subjects and for mortality, we found 18 trials, representing 2748 subjects. The trials are listed in Table 1. Resulting pPREDICTS-tPA models are shown below.

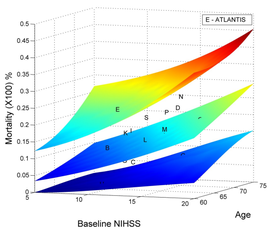
| mRS 0-2 Studies | Time Window (hrs) | Letter |
|---|---|---|
| | | |
| ECASS 3 | 4.5 | A |
| ARTIS | 3 | B |
| Cerebrolysin-tPA | 3 | C |
| CLEAR | 3 | D |
| ECASS II | 6 | F |
| ATLANTIS | 5 | G |
| TUCSON | 3 | H |
| ALIAS1-T | 3 | I |
| Tenecteplase (Aus) | 3 | K |
| Synthesis-Expansion | 4.5 | L |
| EPITHET-Tpa | 6 | 0 |
| Synthesis | 3 | P |
| IMS III | 4.5 | Q |
| CLOTBUST | 3 | R |
| CLEARER | 3 | S |
| | | |
| **Mortality (only)** | **Time Window** | **Letter** |
| | | |
| ATLANTIS A | 6 | E |
| CLASS_T | 6 | J |




pPREDICTS-tPA good functional outcome (mRS0-2; $r^2$ = .85) and mortality ($r^2$ = .54) with respect to baseline NIHSS and age. The pooled model based on the tPA arms of 16-18 RCTs is the middle surface surrounded by prediction intervals at the p<.05 level. Studies whose outcomes are above the upper surface on mRS 0-2 function would be considered to have improved outcome relative to tPA. Mortality below the lower surface would be expected to have worsened mortality .

## Results




Five studies were above the upper p<.05 surface suggesting improvement over tPA alone pooled model at their respective baseline NIHSS and age.
**Cerebrolysin** (3 hour window). A neuroprotectant interpreted as negative, although baseline NIHSS was higher in the treatment arm than the placebo arm, possibly masking a positive effect.
**TUCSON**: (3 hour window). Therapeutic ultrasound plus systemic bubbles to enhance clot lysis. Treatment arm had 4 point higher baseline NIHSS.
**CLOTBUST** (3 hour window). Therapeutic ultrasound without bubbles.
**SYNTHESIS** (3 hour window). Direct to intra-arterial tPA.
**Tenecteplase (Australia)**. (6 hour window; average treatment time 3.1 hours). CT perfusion guided thrombolytic. Excluded internal carotid and basilar artery occlusion.
**NOTABLE NEGATIVES for improved functional outcome**
**SYNTHESIS Expansion**: 4.5 hour time window
**IMS III**: intravenous tpa plus endovascular: 4.5 hour time window
**HIGHER MORTALITY**: Atlantis (6 hour time window) IV tPA

## Discussion

1. **We were able to generate a pooled model for good functional outcome and mortality after rt-PA.**
2. **No endovascular intervention improved outcome following 3 hours.**
3. **Of all the agents that appeared to improve outcome, the time window was mostly at 3 hours. Tenecteplase the only exception and but actually had a comparable average treatment time window (3.1 hours).**
4. **For the time being, 3 hours appears to be a ceiling, just as it is in the cardiac literature for being able to *improve upon* intravenous rt-PA**
5. **As technology advances, there may be more opportunity to improve tPA outcomes with endovascular and neuroprotective interventions.**

## References

**Mandava P, Kent TA.** A method to determine stroke trial success using multidimensional pooled control functions. *Stroke*. **40**, 1803-10 (2009).
**Mandava, P., Krumpelman, C. S., Murthy, S. B. & Kent, T. A**. A critical review of stroke trial analytical methodology: outcome measures, study design, and correction for imbalances. In *Translational Stroke Research: From Target Selection to Clinical Trials* (ed Paul A. Lapchak and John H. Zhang) Ch. 40, 833-861 (Springer, 2012).