Prior Use of Intravenous rt-PA Improves Outcome in Endovascular Stent Retriever Trials for Acute Large Vessel Ischemic Stroke

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Background: Results of randomized clinical trials (RCTs) of endovascular stent-retriever (ESR) trials have mostly shown improved outcomes. However, inclusion and exclusion criteria for these trials and the individual case series that preceded them differ considerably. A major difference between these trials was the extent of intravenous thrombolysis (IVT) with rt-PA prior to endovascular intervention. We therefore applied a method we developed for clinical trial analysis (pPREDICTS, pooled **P**lacebo **Re**sponse **Dic**tates **T**reatment **S**uccess) associating baseline factors with outcome from an aggregation of the placebo arms of RCTs to generate a pPREDICTS model from trial arms based on different percentages of rt-PA use. We show the successful generation of a pPREDICTS model correlating baseline NIHSS and % utilization of rt-PA with good functional outcome (modified Rankin Scale 0-2) and mortality. We take advantage of this pooled arm to generate plots of ESR trials to determine the best and worst performers compared to this "pseudo-control" arm.

Methods: We employed our previously published method (Mandava and Kent, *Stroke* '09) to develop a model based on 55 RCTS representing >11000 subjects that included various percentage of patients receiving IV rt-PA and their baseline NIHSS. We generated multi-dimensional "prediction" intervals (p=.05) to assess difference from predicted outcomes. We compared case series (n=15) of stent retrievers and recently completed stent retriever trials (n=6) against the model directly and through funnel plots (Duval and Tweedie, '02) of case series vs. the pooled control arm.

Results: **Figs 1** shows the outcome model for mRS0-2 and mortality (r^2 =.83/.65 respectively; p<.001). The middle surface is outcome model relating the 2 factors to outcome. The upper and lower surfaces are the ±95% prediction interval surfaces that a study needs to overcome to be considered positive. Individual RCT results are superimposed on this model at the study's own median baseline NIHSS and % rt-PA use. Better outcomes are seen as % rt-PA use increased (along y axis). In **Fig. 2,** all RCTs had outcomes above the p=.05 upper surface, indicating significant improvement. Notably, the greater the % received rt-PA the better the outcome, with the most improvement in studies with 100% rt-PA use (e.g. SWIFT-PRIME). Mortality was higher than expected only in TREVO. Analysis of funnel plots showed quartile of trials with the highest rt-PA use and faster time to recanalization had the best outcomes.

Fig 1a&b. Good outcome (r^2=.79, p<0.001) and mortality (r^2=.58, p<0.001) models based on % IV rt-PA (y axis) and baseline NIHSS (x axis) from individual arms of RCTs. Middle surface: relationship between baseline NIHSS%, tPA and (a) mRS 0-2 and (b) mortality. Upper and Lower surfaces: ±95% prediction intervals. Both models show the influence of % rt-PA: with increasing use of rt-PA there is a higher percentage with a good functional outcome and slightly lower mortality.

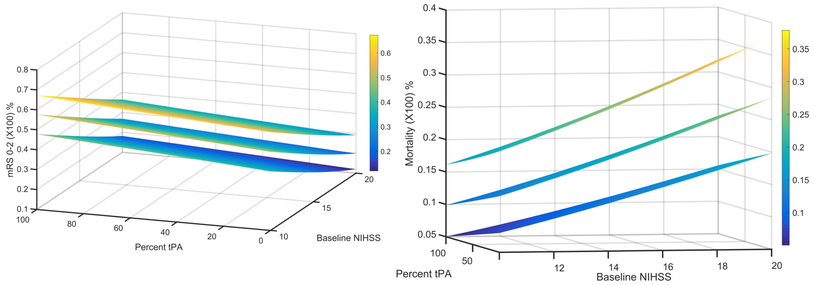


Fig 2a&b. Stent Retriever RCT good outcomes and mortality plotted onto models ranked by the use of IV-rt-PA in their treatment arms. In 2a, all studies are above the p=.05 upper interval (indicating better than expected outcomes at their own baseline characteristics). The best chance of good outcome and lower mortality in trials were in trials with the greatest use of IV rt-PA (e.g. SWIFT-PRIME and EXTEND).

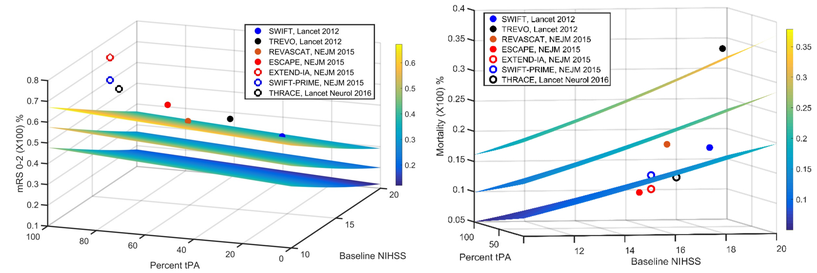
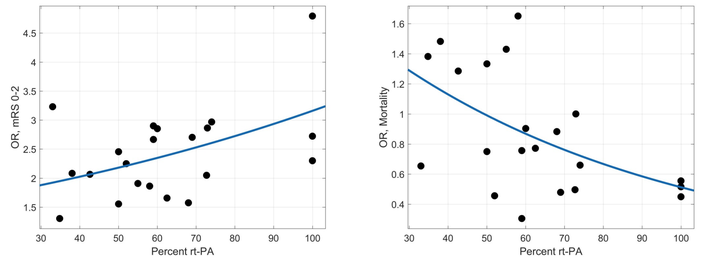


Fig. 3a. Best fit exponential model for odds ratio of good outcome (y axis) showed a significant relationship to increasing rt-PA use (x axis). r^2=0.22, p=0.03. The exponential fit for time to recanalization vs good outcome was not robust (r^2=0.12; p=0.12; Figure not shown). Fig 3b Best fit exponential model for odds ratio of mortality vs. percent rt-PA (r^2=0.28, p=0.014). The fit for time to recanalization and mortality was also significant (r^2=0.21; p=0.03; Figure not shown).



Conclusions:

1. Our analysis supports that all 7 RCTs of stent retriever intervention show benefit in terms of improved good functional outcome compared to control arms at their baseline NIHSS and % rt-PA usage. The trial with higher than expected mortality had among the lowest concomitant use of IV rt-PA.
2. Seven stent retriever RCTs and 14 case series showed a greater chance of good outcome the higher the percent use of IV rt-PA prior to intervention.
3. Time to revascularization was not significantly correlated with good outcome but showed increasing mortality with increasing time to recanalization.
4. It is not clear whether this striking relationship of good outcome to IV rt-PA is due to specific inclusion criteria, but **our results suggest strongly that timely IV rt-PA administration should not be sacrificed in order to go directly to endovascular intervention.**

References

1. Mandava P, Kent TA. A method to determine stroke trial success using multidimensional pooled control functions. Stroke. 2009;40:1803-10.
2. Duval S & Tweedie R (2000), Trim and Fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics, 56, 455–463.

No conflicts: Supported by the State of Texas (Lone Star Stroke Research Network), Department of Veterans Affairs VSIN 16 Pilot grant program, and the Institute for Clinical and Translational Research, Baylor College of Medicine