# Critical Review Form
## Therapy
## Simon JE, et al. Is Intravenous Recombinant Tissue Plasminogen Activator (rt-PA) Safe for Use in Patients Over 80 Years Old with Acute Ischaemic Stroke?- The Calgary Experience, Age Ageing 2004: 33: 143-149

**Objective**: **Assess the utility of IV rt-PA in acute ischemic stroke (AIS) < 3 hours after symptom onset (NINDS protocol) in those over age 80 for the outcomes of National Institute of Health stroke scale and modified Rankin Scale at 3 months, as well as post-treatment bleeding complications.**
**Methods**: **Retrospective, observational study utilizing pre-existing database of patients presenting to Foot Hills Hospital (Calgary) Stroke Unit between April 1996 and June 2002.**

| Guide | | Comments |
|---|---|---|
| **I.** | **Are the results valid?** | |
| **A.** | **Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?** | |
| 1. | Were patients randomized? | No, this is a retrospective, observational study. |
| 2. | Was randomization concealed (blinded)? | Not randomized. |
| 3. | Were patients analyzed in the groups to which they were randomized? | Not randomized. |
| 4. | Were patients in the treatment and control groups similar with respect to known prognostic factors? | No treatment and control groups in an observational study. It would have been useful to compare those over 80 treated at this stroke center who were not thrombolyzed, but the author's choose instead to use historical comparisons. |
| **B.** | **Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?** | |
| 1. | Were patients aware of group allocation? | Yes. |
| 2. | Were clinicians aware of group allocation? | Yes. |
| 3. | Were outcome assessors aware of group allocation? | Not the Neuroradiologist who provided the ASPECTS CT stroke severity score (p. 144). |
| 4. | Was follow-up complete? | One patient lost to follow-up. Other missing data included 16/62 with no pre-treatment Rankin score and 12/62 with no original CT for review (used CT report instead). |

| II. | What are the results (answer the questions posed below)? | |
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| 1. | How large was the treatment effect? | There were two components of treatment effect analyzed: harm and benefit.<br>a) **Harm** – 6 significant intracranial hemorrhages (ICH, defined as CT detected blood with associated clinical deterioration or ≥ 4 point increase in NIHSS) representing 9.7% of cohort (95% CI, 3.6-19.9%) with three fatal ICH within 48 hours of treatment.<br>Note: Among those 6 were 2 NINDS protocol violations.<br>Overall, 24.2% died during the index hospitalization and 32.8% died during 3 month follow-up. These in-hospital mortality rates are comparable with historical cohorts: European BIOMED (23%), Arboix (27%), Tanne (20%), and pre-tPA Canadian data (27%) for those over age 80.<br>b) **Benefit** – median length of stay 13 days, 3 month mRS 4, NIHSS 9. 34% of cohort had improved NIHSS by greater than 10 units. At 3 months 22% of cohort had good outcome (NIHSS 0 or 1, functionally independent), which is lower than NINDS rate (all ages) of 31%. In a non-randomized design, it is uncertain whether this less impressive improvement represents diminished efficacy in the elderly or the more dire impact of stroke in older patients. |
| 2. | How precise was the estimate of the treatment effect? | See Confidence Intervals Table 1 & 2. |

| III. | How can I apply the results to patient care (answer the questions posed below)? | |
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| 1. | Were the study patients similar to my patient? | Yes. |
| 2. | Were all clinically important outcomes considered? | No. Quality of life, interval dispositions (home, rehab hospital, long-term care facility), and patient preferences not reported. |
| 3. | Are the likely treatment benefits worth the potential harm and costs? | Yes! Future research should strive to identify which patients over age 80 who meet NINDS protocol are most likely to receive > 10 point improvement in 3 month NIHSS. |

**Limitations**:
1) Not a randomized controlled trial. This paper represents an important piece of "best-evidence Emergency Medicine" however, because with the exception of NINDS (which had mean age under 70 years) all previous stroke rt-PA trials (ECASS, ECASS II, ATLANTIS) specifically excluded those over age 80.
2) External validity questionable. Calgary represents an experienced stroke center. Their results might not be reproduced at less experienced stroke centers.
3) Inadequate data description. Specifically, they don't attempt to compare those not thrombolyzed at their center with those who are. In addition, they have a significant amount of missing data (pre-treatment Rankin scores and CT scans).

**Bottom Line**: Randomized controlled trials of rt-PA in AIS utilizing NINDS protocol in those over age 80 are necessary (underway, though utilizing 6 hour treatment window, see http://www.dcn.ed.ac.uk/ist3/) to better delineate efficacy and harm, however, this paper suggests that rt-PA by an experienced stroke center does not increase death rates compared with historical cohorts. NIHSS outcomes (functional independence) is not improved in this population to the same extent as in younger cohorts in previous trials, but whether this represents a diminished efficacy or illness severity effect is uncertain.