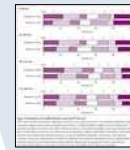


Derived mRS distributions

nLVO

| mRS | Pre-stroke | IVT at time zero | IVT at no-effect time | No treatment |
|-----|------------|------------------|-----------------------|--------------|
| 0 | 0.583 | 0.445 | 0.196 | 0.198 |
| 1 | 0.163 | 0.197 | 0.259 | 0.262 |
| 2 | 0.104 | 0.110 | 0.119 | 0.120 |
| 3 | 0.101 | 0.110 | 0.127 | 0.128 |
| 4 | 0.042 | 0.079 | 0.146 | 0.148 |
| 5 | 0.007 | 0.026 | 0.061 | 0.062 |
| 6 | 0.000 | 0.033 | 0.092 | 0.082 |

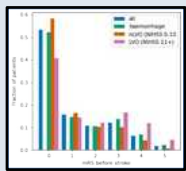
Intravenous alteplase meta-analysis
Lees et al. 2010



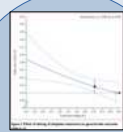
"placebo" population mRS distributions for nLVO and LVO patients combined.

SAMuel-1 survey

Pre-stroke patient mRS scores.



Alteplase meta-analysis
Embersson et al. 2014



Decline of odds ratio of good outcome with time.



Mortality rates with and without IVT.



NIHSS < 11 probabilities of good outcome.

| mRS | IVT at time zero | IVT at no-effect time |
|-----|------------------|-----------------------|
| 0 | 0.140 | 0.048 |
| 1 | 0.093 | 0.076 |
| 2 | 0.128 | 0.131 |
| 3 | 0.161 | 0.159 |
| 4 | 0.208 | 0.239 |
| 5 | 0.108 | 0.130 |
| 6 | 0.162 | 0.217 |

| mRS | Pre-stroke |
|-----|------------|
| 0 | 0.408 |
| 1 | 0.144 |
| 2 | 0.120 |
| 3 | 0.166 |
| 4 | 0.118 |
| 5 | 0.044 |
| 6 | 0.000 |

| mRS | No treatment |
|-----|--------------|
| 0 | 0.050 |
| 1 | 0.079 |
| 2 | 0.136 |
| 3 | 0.164 |
| 4 | 0.247 |
| 5 | 0.135 |
| 6 | 0.189 |

| mRS | MT at time zero | MT at no-effect time |
|-----|-----------------|----------------------|
| 0 | 0.306 | 0.048 |
| 1 | 0.123 | 0.076 |
| 2 | 0.119 | 0.131 |
| 3 | 0.159 | 0.157 |
| 4 | 0.144 | 0.237 |
| 5 | 0.064 | 0.130 |
| 6 | 0.085 | 0.221 |

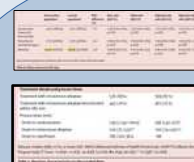
LVO

mRS distribution of control population.



HERMES thrombectomy meta-analysis
Goyal et al. 2016

Mortality rate with MT and average time to MT.



Recanalisation meta-analysis
Hui et al. 2020

75% weight for pre-stroke mRS distribution.

"Our traditional meta-analysis yielded a pooled rate of successful recanalization for IVT+MT of 75% (95% CI, 65%–83%; Figure X1C in the Data Supplement)."

Pre-stroke

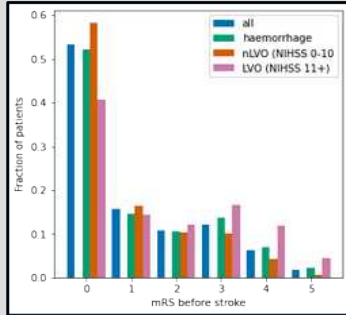
Data sources

SAMueL-1 survey

Data: pre-stroke patient mRS scores.

Location: SAMueL-1 online book, "Additional analysis (not in NIHR report) / Analysis of pre-stroke modified Rankin Scale"

https://samuel-book.github.io/samuel-1/descriptive_stats/08_prestroke_mrs.html



RACE scale

de la Ossa Herrero et al. 2013

Info: NIHSS ≤ 10 for nLVO and NIHSS ≥ 11 for LVO.

Location: final sentence of "Results" section.

"Best overall accuracy [for LVO prediction] for the NIHSS scale was achieved for a score ≥ 11 , with a sensitivity 0.88, specificity 0.72, and overall accuracy 0.76."

Method

1. Collect data.

Take SAMueL-1 survey data for patients with ischaemic stroke only.

The data includes pre-stroke mRS scores.

2. Split into nLVO and LVO.

Split the data into two groups using the NIHSS scale cutoff:

- LVO with NIHSS greater than 10 (≥ 11)
- nLVO with NIHSS of 10 or less (< 11)

3. Find the proportions of each group with each mRS score.

→ Result:

| nLVO pre-stroke | | LVO pre-stroke | |
|-----------------|-------------|----------------|-------------|
| mRS | Probability | mRS | Probability |
| 0 | 0.583 | 0 | 0.408 |
| 1 | 0.163 | 1 | 0.144 |
| 2 | 0.104 | 2 | 0.120 |
| 3 | 0.101 | 3 | 0.166 |
| 4 | 0.042 | 4 | 0.118 |
| 5 | 0.007 | 5 | 0.044 |
| 6 | 0.000 | 6 | 0.000 |

LVO - no treatment

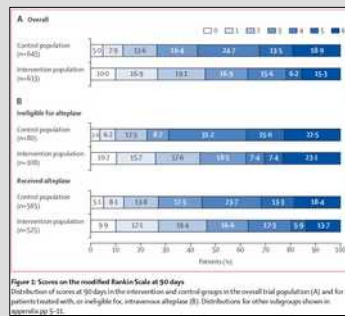
Data sources

Method

HERMES thrombectomy meta-analysis Goyal et al. 2016

Data: mRS distribution of control population.

Location: Figure 1, Group A: Overall, bar labelled “Control Population”).



1. Collect data.

Use the “Control population” set of data with no changes.

→ **Result:**

| LVO no treatment | |
|---------------------|-------------|
| mRS | Probability |
| 0 | 0.050 |
| 1 | 0.079 |
| 2 | 0.136 |
| 3 | 0.164 |
| 4 | 0.247 |
| 5 | 0.135 |
| 6 | 0.189 |

nLVO - no treatment

Data sources

Method

Intravenous alteplase meta-analysis Lees et al. 2010

Data: "placebo" population mRS distributions for nLVO and LVO patients combined.

Location: Figure 2, all "placebo" bars.

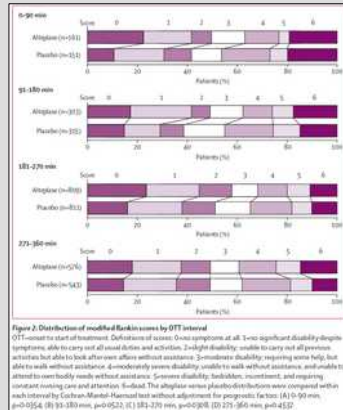


Figure 2. Distribution of modified Rankin scores by OTT interval. OTT—onset to start of treatment. Definitions of scores: 0=no symptoms at all; 1=no significant disability despite symptoms, able to carry out all usual duties and activities; 2=slight disability, unable to carry out all previous activities but able to look after one's own needs without assistance; 3=moderate disability, requiring some help, but able to walk without assistance; 4=moderately severe disability, unable to walk without assistance, and unable to attend to one's bodily needs without assistance; 5=severe disability, bedridden, incontinent, and requiring constant nursing care and attention; 6=dead. The alteplase versus placebo distributions were compared within each interval by Cochran-Mantel-Haenszel test without adjustment for prognostic factors. (A) 0-99 min, $p=0.054$; (B) 100-149 min, $p=0.023$; (C) 150-199 min, $p=0.008$; (D) 200-249 min, $p=0.432$.

1. Collect data.

The sizes of the bars are not given in the text.

- 1) Measure the number of pixels in each section of each "Placebo" bar in the image.
- 2) Combine the bars and scale so that they sum to 1.

→ Result:

| nLVO & LVO no treatment | |
|----------------------------|-------------|
| mRS | Probability |
| 0 | 0.149 |
| 1 | 0.202 |
| 2 | 0.125 |
| 3 | 0.140 |
| 4 | 0.181 |
| 5 | 0.086 |
| 6 | 0.118 |

2. Find a reference probability.

| Baseline NIHSS score | Number of patients with mRS 0 or 1 | Total number of patients |
|----------------------|------------------------------------|--------------------------|
| 0-4 | 189 | 321 |
| 5-10 | 538 | 1252 |
| Total: | 727 | 1573 |

The proportion 727 out of 1573 is 46%.

→ Probability $P(mRS \leq 1) = 0.46$

3. Remove the LVO patients.

To reach $P(mRS \leq 1) = 0.46$ in the nLVO-only distribution, use the following weighted distributions:

- 1) Scale the "nLVO & LVO" distribution up to 149%.
- 2) Scale the "LVO" distribution down to 49%.
- 3) Take the difference to leave only the "nLVO" patients.

→ Result:

| nLVO no treatment | |
|----------------------|-------------|
| mRS | Probability |
| 0 | 0.198 |
| 1 | 0.262 |
| 2 | 0.120 |
| 3 | 0.128 |
| 4 | 0.148 |
| 5 | 0.062 |
| 6 | 0.082 |

RACE scale de la Ossa Herrero et al. 2013

Info: NIHSS ≤ 10 for nLVO and NIHSS ≥ 11 for LVO.

Location: final sentence of "Results" section.

"Best overall accuracy [for LVO prediction] for the NIHSS scale was achieved for a score ≥ 11 , with a sensitivity 0.88, specificity 0.72, and overall accuracy 0.76."

Alteplase meta-analysis Emberson et al. 2014

Data: NIHSS < 11 probabilities of good outcome.

Location: Figure 2, "Control" column, "Baseline NIHSS score" rows "0-4" and "5-10".

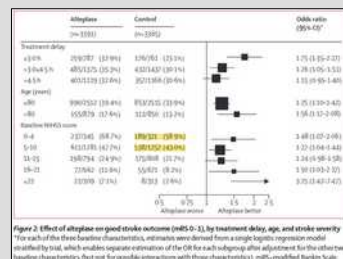


Figure 2. Effect of alteplase on good stroke outcome (mRS 0-1), by treatment delay, age, and stroke severity. For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics. Data not for possible interactions with those characteristics. mRS—modified Rankin Scale.

mRS distribution as calculated earlier.

| LVO no treatment | |
|------------------|-------------|
| mRS | Probability |
| 0 | 0.050 |
| 1 | 0.079 |
| 2 | 0.136 |
| 3 | 0.164 |
| 4 | 0.247 |
| 5 | 0.135 |
| 6 | 0.189 |

Sanity check – nLVO / LVO split

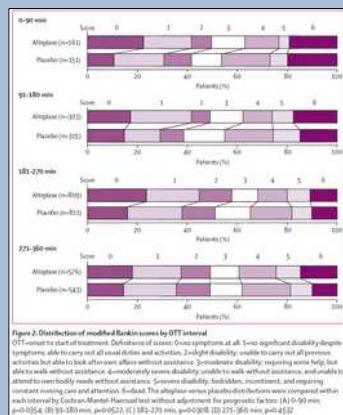
Data sources

Method

Intravenous alteplase meta-analysis Lees et al. 2010

Data: “placebo” population mRS distributions for nLVO and LVO patients combined.

Location: Figure 2, all “placebo” bars.



IST-3 thrombolysis clinical trial Sandercock et al. 2012

Data: proportions of patients with nLVO and LVO.

Location: Table 1, “NIHSS”

| NIHSS† | 304 (20%) | 308 (20%) |
|--------|-----------|-----------|
| 0-5 | 422 (28%) | 430 (28%) |
| 6-10 | 306 (20%) | 295 (19%) |
| 11-15 | 270 (18%) | 273 (18%) |
| 16-20 | 213 (14%) | 214 (14%) |

RACE scale de la Ossa Herrero et al. 2013

Info: NIHSS ≤ 10 for nLVO and NIHSS ≥ 11 for LVO.

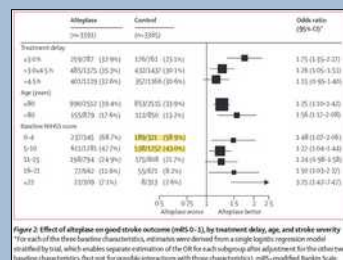
Location: final sentence of “Results” section.

“Best overall accuracy [for LVO prediction] for the NIHSS scale was achieved for a score ≥ 11 , with a sensitivity 0.88, specificity 0.72, and overall accuracy 0.76.”

Alteplase meta-analysis. Emberson et al. 2014

Data: numbers of patients by NIHSS score.

Location: Figure 2.



Excess deaths - IVT

Data sources

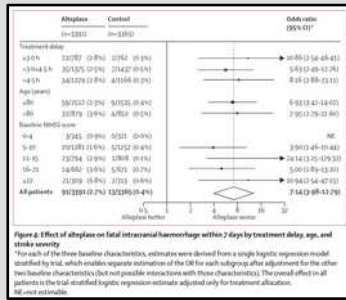
Method

Alteplase meta-analysis

Emberson et al. 2014

Data: Mortality rates with and without IVT.

Location: Figure 4, "Alteplase" and "Control" columns, "Baseline NIHSS score" section, rows labelled "0-4" and "5-10".



1. Calculate excess deaths for nLVO patients.

| | Given IVT | | | No treatment | | |
|--------------------|-----------|------|-------|--------------|------|-------|
| NIHSS → | 0-4 | 5-10 | 0-10 | 0-4 | 5-10 | 0-10 |
| Number of patients | 345 | 1281 | 1626 | 321 | 1252 | 1573 |
| Deaths | 3 | 20 | 23 | 0 | 5 | 5 |
| % deaths | | | 1.41% | | | 0.32% |

Excess deaths is the difference in percentages.

→ **Excess death is 1.1%.**

2. Calculate excess deaths for LVO patients.

| | Given IVT | | | |
|--------------------|-----------|-------|-----|-------|
| NIHSS | 11-15 | 16-21 | ≥22 | ≥11 |
| Number of patients | 794 | 662 | 309 | 1765 |
| Deaths | 23 | 24 | 21 | 68 |
| % deaths | | | | 3.85% |

| | No treatment | | | |
|--------------------|--------------|-------|-----|-------|
| NIHSS | 11-15 | 16-21 | ≥22 | ≥11 |
| Number of patients | 808 | 671 | 313 | 1792 |
| Deaths | 1 | 5 | 2 | 8 |
| % deaths | | | | 0.45% |

Excess deaths is the difference in percentages.

→ **Excess death is 3.4%.**

RACE scale

de la Ossa Herrero et al. 2013

Info: NIHSS ≤10 for nLVO and NIHSS ≥11 for LVO.

Location: final sentence of "Results" section.

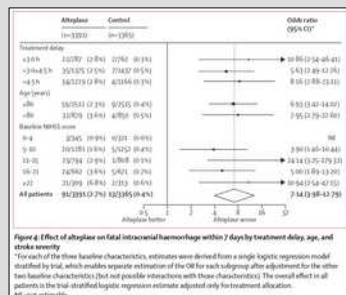
"Best overall accuracy [for LVO prediction] for the NIHSS scale was achieved for a score ≥11, with a sensitivity 0.88, specificity 0.72, and overall accuracy 0.76."

Alteplase meta-analysis

Emberson et al. 2014

Data: Mortality rates with and without IVT.

Location: Figure 4, "Alteplase" and "Control" columns, "Baseline NIHSS score" section, rows labelled "11-15", "16-21" and "≥22".



nLVO – IVT at no-effect time

Data sources

IVT excess deaths
as calculated earlier.

1.1%

mRS distribution
as calculated earlier.

| nLVO no treatment | |
|-------------------|-------------|
| mRS | Probability |
| 0 | 0.198 |
| 1 | 0.262 |
| 2 | 0.120 |
| 3 | 0.128 |
| 4 | 0.148 |
| 5 | 0.062 |
| 6 | 0.082 |

Method

1. Apply excess deaths to “no treatment” distribution.

For a population treated at the time of no effect, expect no improvement compared with the no-treatment distribution but for some additional deaths.

Assume excess death is equally likely for all patients.

| mRS | nLVO no treatment | 1.1% deaths | nLVO no treatment with excess deaths |
|-----|-------------------|-------------|--------------------------------------|
| 0 | 0.198 | -0.002 | 0.196 |
| 1 | 0.262 | -0.003 | 0.259 |
| 2 | 0.120 | -0.001 | 0.119 |
| 3 | 0.128 | -0.001 | 0.127 |
| 4 | 0.148 | -0.002 | 0.146 |
| 5 | 0.062 | -0.001 | 0.061 |
| 6 | 0.082 | +0.010 | 0.092 |

→ **Result:**

| nLVO IVT at no-effect time | |
|-------------------------------|-------------|
| mRS | Probability |
| 0 | 0.196 |
| 1 | 0.259 |
| 2 | 0.119 |
| 3 | 0.127 |
| 4 | 0.146 |
| 5 | 0.061 |
| 6 | 0.092 |

Patient transport model

Holodinsky et al. 2018

Data: decline of chance of
good outcome (mRS ≤ 1)
with time to thrombolysis.

| Non-Large-Vessel Occlusion | |
|--------------------------------------|--|
| P(mRS 0 - 1 alteplase and OTT = x) | $0.6343 - 0.00000005x^2 - 0.0005x$; minimum value = 0.4622 |

Location: Table, “Non-Large-Vessel Occlusion” section

Sanity check

In the patient transport model, for IVT at the time of no effect the probability $P(\text{mRS} \leq 1) = 0.4622$.

The equivalent measure from the above distribution is $P(\text{mRS} \leq 1) = 0.196 + 0.259 = 0.455$.

LVO – IVT at no-effect time

Data sources

IVT excess deaths
as calculated earlier.

3.4%

mRS distribution
as calculated earlier.

| LVO no treatment | |
|------------------|-------------|
| mRS | Probability |
| 0 | 0.050 |
| 1 | 0.079 |
| 2 | 0.136 |
| 3 | 0.164 |
| 4 | 0.247 |
| 5 | 0.135 |
| 6 | 0.189 |

Method

1. Apply excess deaths to “no treatment” distribution.

For a population treated at the time of no effect, expect no improvement compared with the no-treatment distribution but for some additional deaths.

Assume excess death is equally likely for all patients.

| mRS | LVO no treatment | 3.4% deaths | LVO no treatment with excess deaths |
|-----|------------------|-------------|-------------------------------------|
| 0 | 0.050 | -0.002 | 0.048 |
| 1 | 0.079 | -0.003 | 0.076 |
| 2 | 0.136 | -0.004 | 0.131 |
| 3 | 0.164 | -0.005 | 0.159 |
| 4 | 0.247 | -0.008 | 0.239 |
| 5 | 0.135 | -0.004 | 0.130 |
| 6 | 0.189 | +0.027 | 0.217 |

→ **Result:**

| LVO IVT at no-effect time | |
|------------------------------|-------------|
| mRS | Probability |
| 0 | 0.048 |
| 1 | 0.076 |
| 2 | 0.131 |
| 3 | 0.159 |
| 4 | 0.239 |
| 5 | 0.130 |
| 6 | 0.217 |

Excess deaths - MT

Data sources

Method

HERMES
thrombectomy
meta-analysis
Goyal et al. 2016

Data: Mortality rate with MT
and average time to MT.

Locations:
Mortality rate: Table 4.
Time: Table 1.

Recanalisation meta-analysis Hui et al. 2020

Info: 75% weight for pre-stroke mRS distribution.

Location: "Secondary Outcome: Recanalization" section, final sentence.

| | Interventive population | Control population | Baseline age (years) | Baseline rates (2013) | Follow-up rates (2013) | Adjusted rates (2013) | Adjusted rates (2013) |
|--------------------|-------------------------|--------------------|----------------------|-----------------------|------------------------|-----------------------|-----------------------|
| Longest survival | 4.4 (22.0) | 4.4 (22.0) | 5.1 | 1.48 (95% CI) | 1.27 (95% CI) | 1.07 (95% CI) | 1.27 (95% CI) |
| Shortest survival | 0.5 (2.0) | 0.5 (2.0) | 5.1 | 1.48 (95% CI) | 1.27 (95% CI) | 1.07 (95% CI) | 1.27 (95% CI) |
| Median survival | 1.9 (0.9) | 1.9 (0.9) | 5.1 | 1.48 (95% CI) | 1.27 (95% CI) | 1.07 (95% CI) | 1.27 (95% CI) |
| Standard deviation | 0.5 (0.5) | 0.5 (0.5) | 5.1 | 1.48 (95% CI) | 1.27 (95% CI) | 1.07 (95% CI) | 1.27 (95% CI) |

Note: Values are median (95% CI).

Treatment details and outcomes

| Treatment with intravenous atezolizumab | 3.8 (2.9) | 3.66 (2.7) |
|---|------------|------------|
| Treatment with intravenous atezolizumab documented within 30s | 4.02 (2.9) | 4.03 (2.9) |

Proportion (95% CI)

| Event to randomization | 1.95 (1.04)–2.90 (1.0) | 1.96 (1.04)–2.90 (1.0) |
|-----------------------------------|------------------------|------------------------|
| Event to intravenous atezolizumab | 1.00 (0.75)–1.31 (1.0) | 1.00 (0.75)–1.40 (1.0) |
| Event to randomization | NA | NA |

Note: Values are median (95% CI).

Table 1. Baseline characteristics in the pooled data

“Our traditional meta-analysis yielded a pooled rate of successful recanalization for IVT+MT of 75% (95% CI, 65%–83%; Figure XIC in the Data Supplement).”

mRS distributions
as calculated earlier.

| | LVO pre-stroke | LVO no treatment |
|-----|----------------|------------------|
| mRS | Probability | Probability |
| 0 | 0.408 | 0.050 |
| 1 | 0.144 | 0.079 |
| 2 | 0.120 | 0.136 |
| 3 | 0.166 | 0.164 |
| 4 | 0.118 | 0.247 |
| 5 | 0.044 | 0.135 |
| 6 | 0.000 | 0.189 |

1. Find reference data point.

The average MT treatment time is 285 minutes and the death rate of patients given MT is 15.3%.

This gives a probability that mRS is less than 6 of 84.7%.

Convert this probability to log-odds. The log-odds of mRS being less than 6 when MT is given at 285 minutes is 1.709.

→ log-odds reference = 1.709

2. Define time-zero distribution.

Calculate two distributions:

- Full-effect data: pre-stroke data with excess deaths.
- No-effect data: no-treatment data with excess deaths.

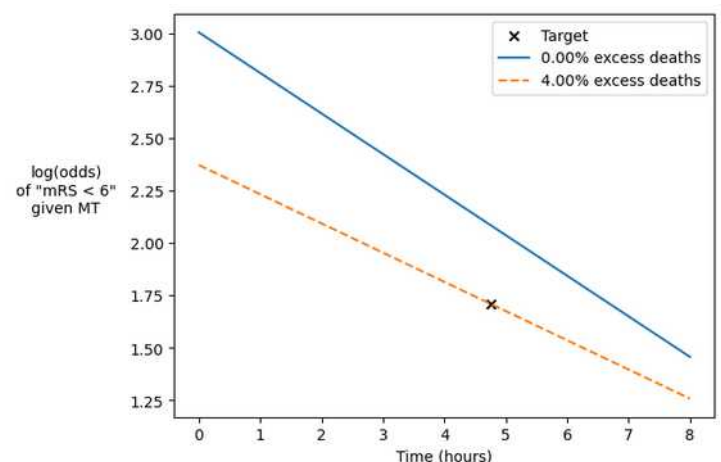
Combine 75% of the full-effect data with 25% of the no-effect data to make the time-zero data.

3. Method for finding excess deaths:

- 1) Set the excess death value e .
- 2) As above, use these excess deaths to calculate:
 - 1) The full-effect data
 - 2) The no-effect-time data
 - 3) The time-zero data
- 3) Take the probability that mRS is less than 6 in the time-zero and the no-effect-time distributions.
- 4) Convert the probabilities to log-odds.
- 5) Plot the two log-odds values and treatment times and connect the points with a straight line.
- 6) How close is the straight line to the reference point?

These steps can be repeated with different values of excess death e until the line passes exactly through the reference data point.

Using an optimiser function, we find the best $e=4.00\%$.



→ **Excess death is 4.0%.**

LVO – MT at no-effect time

Data sources

MT excess deaths
as calculated earlier.

4.0%

mRS distribution
as calculated earlier.

| LVO no treatment | |
|------------------|-------------|
| mRS | Probability |
| 0 | 0.050 |
| 1 | 0.079 |
| 2 | 0.136 |
| 3 | 0.164 |
| 4 | 0.247 |
| 5 | 0.135 |
| 6 | 0.189 |

Method

1. Apply excess deaths to “no treatment” distribution.

For a population treated at the time of no effect, expect no improvement compared with the no-treatment distribution but for some additional deaths.

Use the excess death rate of 4.0%.

Assume excess death is equally likely for all patients.

| mRS | LVO no treatment | 4.0% deaths | LVO no treatment with excess deaths |
|-----|------------------|-------------|-------------------------------------|
| 0 | 0.050 | -0.002 | 0.048 |
| 1 | 0.079 | -0.003 | 0.076 |
| 2 | 0.136 | -0.005 | 0.131 |
| 3 | 0.164 | -0.006 | 0.157 |
| 4 | 0.247 | -0.009 | 0.237 |
| 5 | 0.135 | -0.005 | 0.130 |
| 6 | 0.189 | +0.040 | 0.221 |

→ **Result:**

| LVO MT at no-effect time | |
|-----------------------------|-------------|
| mRS | Probability |
| 0 | 0.048 |
| 1 | 0.076 |
| 2 | 0.131 |
| 3 | 0.157 |
| 4 | 0.237 |
| 5 | 0.130 |
| 6 | 0.221 |

Chance decay over time

Data sources

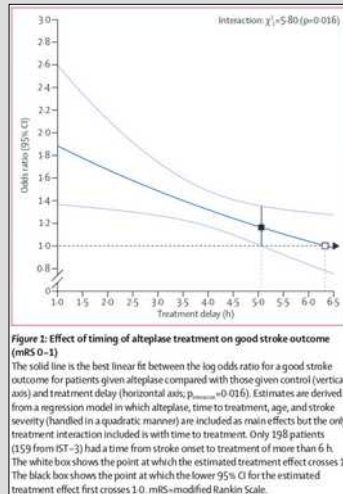
Method

Alteplase meta-analysis

Emberson et al. 2014

Data: decline of odds ratio of good outcome with time for all patients (i.e. any NIHSS score) treated with alteplase compared with a control group.

Location: Figure 1



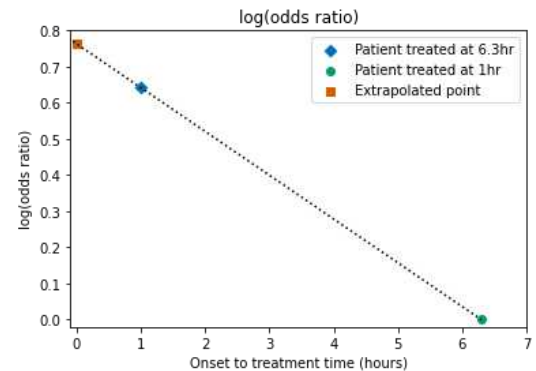
1. Get reference data points

Take two odds ratio points from this chart and convert them to $\log(\text{odds ratio})$, where “log” means “natural log”:

| Treatment delay (hours) | Odds ratio | $\log(\text{odds ratio})$ |
|-------------------------|------------|---------------------------|
| 1.0 | 1.9 | 0.64185 |
| 6.3 | 1.0 | 0.00000 |

2. Straight line fit

Connect the two “ $\log(\text{odds ratio})$ ” and time points with a straight line.



The slope of the line is:

$$b = (0.00000 - 0.64185) \div (6.3 - 1.0)$$

$$b = -0.1211...$$

The line hits time zero at a $\log(\text{odds ratio})$ value:

$$a = 0.76296.$$

3. Convert to probability

If we use a reference probability value, then we can calibrate the straight line fit and use it to calculate a probability of $\text{mRS} \leq 1$ at any time.

For a reference point at the no-effect time t_{ne} , the probability at time zero is:

$$P(\text{mRS} \leq 1 | t = 0) = \frac{e^a \cdot \left\{ \frac{P_R}{1 - P_R} \right\}}{1 + e^a \cdot \left\{ \frac{P_R}{1 - P_R} \right\}}$$

where:

$$P_R = P(\text{mRS} \leq 1 | t_{ne})$$

4. Usage

This straight line fit applies to $\text{mRS} \leq 1$ data only.

The same value of a can be used to fit the decay with time for:

- nLVO and LVO patients combined
- nLVO patients only
- LVO patients only

Alteplase meta-analysis

Emberson et al. 2014

Info: use same slope for all straight line fits.

Location: “Results” section, paragraphs 2 and 3.

“The effect of alteplase on a good outcome was chiefly driven by treatment delay; after controlling for treatment delay, neither age nor severity of stroke contributed significant additional predictive value (appendix p 5).”

nLVO – IVT at time zero

Data sources

Method

mRS distribution
as calculated earlier.

| nLVO IVT at no-effect time | |
|-------------------------------|-------------|
| mRS | Probability |
| 0 | 0.196 |
| 1 | 0.259 |
| 2 | 0.119 |
| 3 | 0.127 |
| 4 | 0.146 |
| 5 | 0.061 |
| 6 | 0.092 |



1. Get reference probability at no-effect time.

Take the probability of mRS being less than or equal to 1. This matches the data that went into the formula for probability at time zero.

$$\rightarrow P(\text{mRS} \leq 1 \mid t=t_{\text{ne}}) = 45.5\%$$

Formula for
probability at time
zero
as calculated earlier.

$$P(\text{mRS} \leq 1 \mid t=0) = \frac{e^a \cdot \left\{ \frac{P_R}{1-P_R} \right\}}{1 + e^a \cdot \left\{ \frac{P_R}{1-P_R} \right\}}$$

$$P_R = P(\text{mRS} \leq 1 \mid t_{\text{ne}})$$

$$a = 0.76296$$



2. Calculate a reference probability at time zero.

Plug the values of a and $P_R=45.5\%$ into the formula.

$$\rightarrow P(\text{mRS} \leq 1 \mid t=0) = 64.2\%$$

IVT excess deaths
as calculated earlier.

1.1%



3. Combine mRS distributions.

To reach $P(\text{mRS} \leq 1 \mid t=0)=0.642$ in the time-zero distribution, use the following weighted distributions:

- 1) Apply the excess deaths to the pre-stroke data.
- 2) Multiply the “pre-stroke data with excess deaths” data by 0.643.
- 3) Multiply the “IVT at no-effect time” data by 0.357.
- 4) Add these two sets of data together.

→ **Result:**

| nLVO IVT at time zero | |
|--------------------------|-------------|
| mRS | Probability |
| 0 | 0.445 |
| 1 | 0.197 |
| 2 | 0.110 |
| 3 | 0.110 |
| 4 | 0.079 |
| 5 | 0.026 |
| 6 | 0.033 |

Patient transport
model

Holodinsky et al. 2018

Data: decline of chance of
good outcome (mRS ≤ 1)
with time to thrombolysis.

| Non-Large-Vessel Occlusion | |
|------------------------------------|--|
| P(mRS 0-1 alteplase and OTT = x) | $0.6343 - 0.00000005 \cdot x^2 - 0.0005 \cdot x$ minimum value = 0.4622 |



Sanity check

In the patient transport model, for IVT at time zero the probability $P(\text{mRS} \leq 1) = 0.6343$.

The equivalent probability from the above distribution is $P(\text{mRS} \leq 1) = 0.642$.

Location: Table, “Non-Large-Vessel Occlusion” section

LVO – IVT at time zero

Data sources

Method

mRS distribution
as calculated earlier.

| LVO IVT at no-effect time | |
|------------------------------|-------------|
| mRS | Probability |
| 0 | 0.048 |
| 1 | 0.076 |
| 2 | 0.131 |
| 3 | 0.159 |
| 4 | 0.239 |
| 5 | 0.130 |
| 6 | 0.217 |



1. Get reference probability at no-effect time.

Take the probability of mRS being less than or equal to 1. This matches the data that went into the formula for probability at time zero.

$$\rightarrow P(\text{mRS} \leq 1 \mid t=t_{\text{ne}}) = 12.4\%$$

Formula for
probability at time
zero
as calculated earlier.

$$P(\text{mRS} \leq 1 \mid t=0) = \frac{e^a \cdot \left\{ \frac{P_R}{1-P_R} \right\}}{1 + e^a \cdot \left\{ \frac{P_R}{1-P_R} \right\}}$$

$$P_R = P(\text{mRS} \leq 1 \mid t_{\text{ne}})$$

$$a = 0.76296$$



2. Calculate a reference probability at time zero.

Plug the values of a and $P_R=12.4\%$ into the formula.

$$\rightarrow P(\text{mRS} \leq 1 \mid t=0) = 23.3\%$$

IVT excess deaths
as calculated earlier.

| |
|------|
| 3.4% |
|------|



3. Combine mRS distributions.

To reach $P(\text{mRS} \leq 1 \mid t=0)=0.233$ in the time-zero distribution, use the following weighted distributions:

- 1) Apply the excess deaths to the pre-stroke data.
- 2) Multiply the “pre-stroke data with excess deaths” data by 0.255.
- 3) Multiply the “IVT at no-effect time” data by 0.745.
- 4) Add these two sets of data together.

→ **Result:**

mRS distribution
as calculated earlier.

| LVO pre-stroke | |
|-------------------|-------------|
| mRS | Probability |
| 0 | 0.408 |
| 1 | 0.144 |
| 2 | 0.120 |
| 3 | 0.166 |
| 4 | 0.118 |
| 5 | 0.044 |
| 6 | 0.000 |



| LVO IVT at time zero | |
|-------------------------|-------------|
| mRS | Probability |
| 0 | 0.140 |
| 1 | 0.093 |
| 2 | 0.128 |
| 3 | 0.161 |
| 4 | 0.208 |
| 5 | 0.108 |
| 6 | 0.162 |

LVO – MT at time zero

Data sources

Recanalisation meta-analysis Hui et al. 2020

Info: 75% weight for pre-stroke mRS distribution.

Location: "Secondary Outcome: Recanalization" section, final sentence.

MT excess deaths as calculated earlier.

mRS distribution as calculated earlier.

mRS distribution as calculated earlier.

"Our traditional meta-analysis yielded a pooled rate of successful recanalization for IVT+MT of 75% (95% CI, 65%–83%; Figure XIC in the Data Supplement)."

4.0%

| LVO pre-stroke | |
|----------------|-------------|
| mRS | Probability |
| 0 | 0.408 |
| 1 | 0.144 |
| 2 | 0.120 |
| 3 | 0.166 |
| 4 | 0.118 |
| 5 | 0.044 |
| 6 | 0.000 |

| LVO MT at no-effect time | |
|--------------------------|-------------|
| mRS | Probability |
| 0 | 0.048 |
| 1 | 0.076 |
| 2 | 0.131 |
| 3 | 0.157 |
| 4 | 0.237 |
| 5 | 0.130 |
| 6 | 0.221 |

Method

1. Define time-zero distribution.

Combine 75% of the full-effect data with 25% of the no-effect data. The full-effect data is the pre-stroke data with the excess deaths as a result of MT.

2. Add excess deaths to pre-stroke distribution.

| mRS | LVO pre-stroke | 4.0% deaths | LVO pre-stroke with excess deaths |
|-----|----------------|-------------|-----------------------------------|
| 0 | 0.408 | -0.016 | 0.392 |
| 1 | 0.144 | -0.006 | 0.138 |
| 2 | 0.120 | -0.005 | 0.115 |
| 3 | 0.166 | -0.007 | 0.160 |
| 4 | 0.118 | -0.005 | 0.113 |
| 5 | 0.044 | -0.002 | 0.042 |
| 6 | 0.0000 | +0.040 | 0.040 |

3. Combine the data for full effect and no effect of recanalisation.

- Multiply the "LVO pre-stroke with excess deaths" data by 0.75.
- Multiply the "LVO MT at no-effect time" data by 0.25.
- Add these two sets of data together.

→ **Result:**

| LVO MT at time zero | |
|---------------------|-------------|
| mRS | Probability |
| 0 | 0.306 |
| 1 | 0.123 |
| 2 | 0.119 |
| 3 | 0.159 |
| 4 | 0.144 |
| 5 | 0.064 |
| 6 | 0.085 |

Sanity check – MT success rate

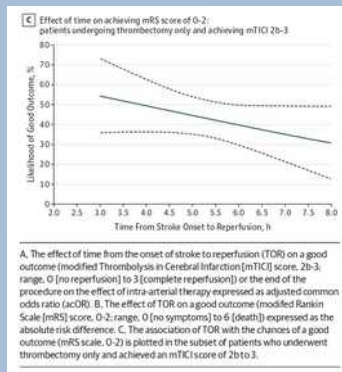
Data sources

Method

MR CLEAN Recanalisation clinical trial Fransen et al. 2016

Data: decline of chance of good outcome (mRS 0-2) with time to thrombectomy for successful reperfusion only.

Location: Figure C, end points of graph stated in “Tertiary analysis” subsection.



1. Extrapolate the line back to time zero.

End points from the graph (given in “Tertiary analysis” section):

| Time (hours) | Probability of mRS 0-2 |
|--------------|------------------------|
| 3.0 | 55% |
| 8.0 | 31% |

Assume the decrease with time is constant and that the graph shows a straight line. This gives an average decrease in probability of 4.8% per hour.

At time zero, the probability would be $55\% + (3 \times 4.8\%) = 69.4\%$.

Pre-stroke probability of mRS 0-2 is: $0.408 + 0.144 + 0.120 = 67.2\%$.

→ **for successful recanalisation, use the full recovery mRS distribution.**

2. Check treatment at 8 hours.

From the graph, the end point is 31%. Scaling down by 0.75 successful recanalisation gives $31\% \times 0.75 = 23.25\%$.

Probability of mRS 0-2 given MT at time of no effect (8 hours) is $0.048 + 0.076 + 0.131 = 25.5\%$.

3. Check treatment at 0 hours.

From the graph, the extrapolated point at time zero is 69.4%. Scaling down by 0.75 successful recanalisation rate, $69.4\% \times 0.75 = 52.05\%$.

MT at time zero probability of mRS 0-2 is: $0.306 + 0.123 + 0.119 = 54.8\%$.

→ **75% successful recanalisation gives a good enough match.**

mRS distribution as calculated earlier.

| LVO pre-stroke | |
|----------------|-------------|
| mRS | Probability |
| 0 | 0.408 |
| 1 | 0.144 |
| 2 | 0.120 |
| 3 | 0.166 |
| 4 | 0.118 |
| 5 | 0.044 |
| 6 | 0.000 |

Recanalisation meta-analysis Hui et al. 2020

Info: 75% weight for pre-stroke mRS distribution.

Location: “Secondary Outcome: Recanalization” section, final sentence.

“Our traditional meta-analysis yielded a pooled rate of successful recanalization for IVT+MT of 75% (95% CI, 65%–83%; Figure XIC in the Data Supplement).”

| mRS | LVO MT at no-effect time | LVO MT at time zero |
|-----|--------------------------|---------------------|
| 0 | 0.048 | 0.306 |
| 1 | 0.076 | 0.123 |
| 2 | 0.131 | 0.119 |
| 3 | 0.157 | 0.159 |
| 4 | 0.237 | 0.144 |
| 5 | 0.130 | 0.064 |
| 6 | 0.221 | 0.085 |

mRS distributions as calculated earlier.