Efficiency of stroke clinical trials with ordinal outcomes: a simulation study

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INTRODUCTION

- Stroke is the second most common cause of death and a major cause of disability worldwide.

- Although at least 178 randomized clinical trials were conducted for 75 promising agents, only 1 agent has been approved by the FDA/EMA (2001).

The gold standard for performing Phase III clinical trials has been to dichotomize the mRS as a good outcome (scores 0 or 1):

0 - **No symptoms.**

1 - **No significant disability.** Able to carry out all usual activities

2 - **Slight disability.** Able to look after own affairs without assistance

3 - **Moderate disability.** Requires some help

4 - **Moderately severe disability.** Needs assistance

5 - **Severe disability.** Requires constant care and attention

6 - **Dead.**

Different alternatives have been proposed:

1. Shift Analysis [Savitz et al, 2007]:
   - Works with the full ordinal scale
2. Responder analysis [Berge et al, 2002]:
   - Dichotomizes the outcome taking into account the initial status of each patient.
3. Global recovery outcome [Dávalos, 2002]:
   - Considers simultaneously information from more than one recovery dichotomized variables.

Objective:

To assess the power of the most common statistical methods used in stroke clinical trials and other *alternatives*.

METHODS

Scales

- The modified Ranking Scale (**mRS**):
  - Measures disability or dependence in daily activities.
  - from 0 (perfect health) to 6 (death).
- The National Institute of Health Stroke Scale (**NIHSS**)
  - Measures neurological status.
  - from 0 (minimal) to 42 (severe deficit).
- The Barthel Index (**BI**)
  - Measures independence in personal care and mobility.
  - from 0 to 100 (independence) by steps of 5.
  - It was transformed as iBI = (100-BI)/5.

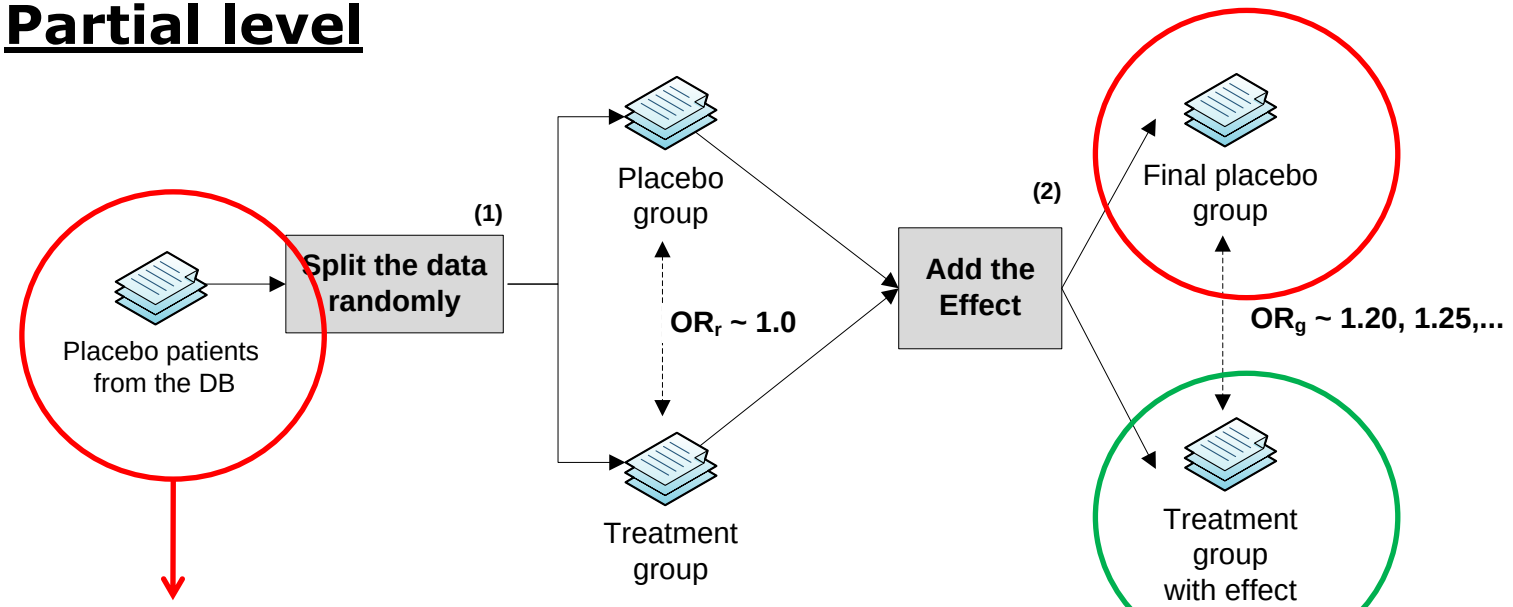
Data

- Pooling database grouping 4 clinical trials performed to assess the efficacy of oral citicoline.
- Applying new eligibility criteria, 1372 patients were selected, 789 randomized to citicoline and 583 to placebo.
- Only placebo data was employed in the simulations.

Addition of the treatment effect

- Using two different strategies:
  - Partial (or patient) level: OAST collaboration, 2008
  - Marginal (or population) level: Choi et al, 1998
- OR=1.20, 1.25, 1.30 and 1.35
- ORs under an ordinal logistic regression (proportional odds)

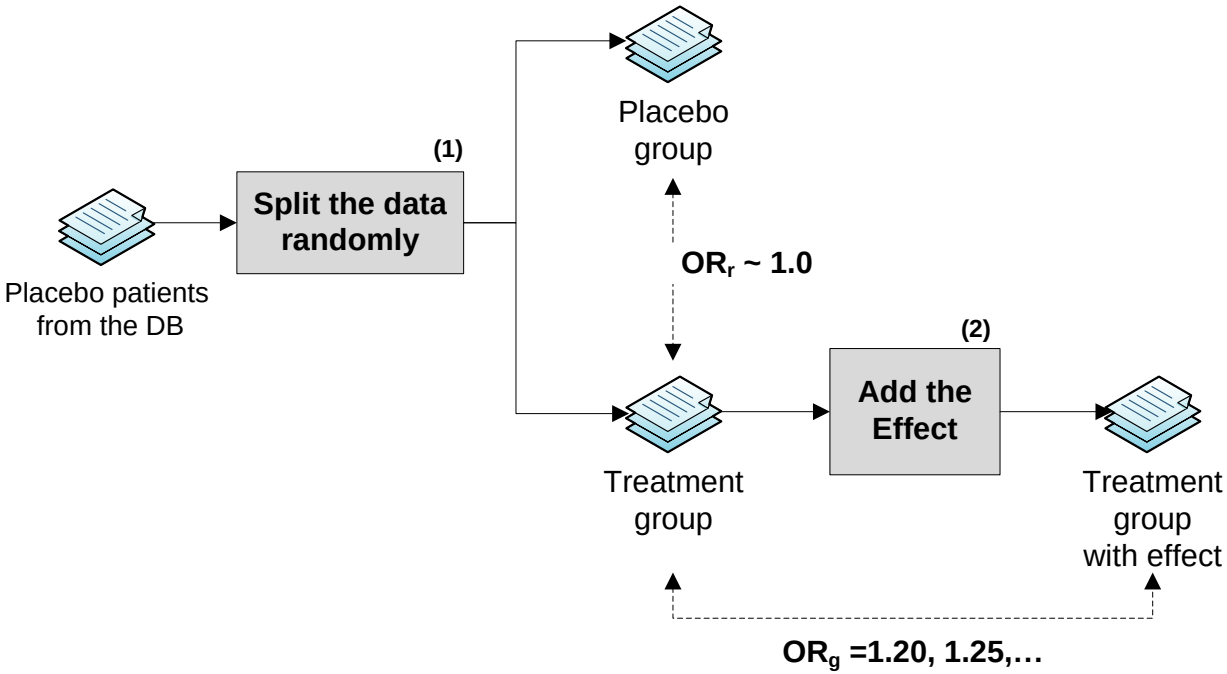
Partial level



$$P(Y \leq j) = \frac{1}{1+\exp(-\alpha_j - \boldsymbol{\beta}'\mathbf{X})}$$

$$P(Y \leq j) = \frac{1}{1+\exp(-\alpha_j - \boldsymbol{\beta}'\mathbf{X} - \log(OR))}$$

Marginal level



Based on an ordinal logistic regression model, a treatment effect is added redistributing the patients within the scores

Example:

tx / mRS	0	1	2	3	4	5	6
Observed	16	30	45	47	72	20	55
		-7 +12	*-6 +18*	*-1 +19*	*+5 +14*	*+3 +11*	*+11*
Target	20.5	36.6	50.9	48.7	66.9	17.1	44.3

Statistical methods to assess treatment effect

- Dichotomized mRS: mRS≤1 and mRS≤2.
- Full ordinal scale: t-test, Wilcoxon-Mann-Whitney test, ordinal logistic regression with proportional odds.
- Responder analysis as proposed by Adams et al. (2004) and Murray et al. (2005)
- A global ad-hoc version of the above methods is employed.
- The effect of adjusting for important prognostic variables in each method is also assessed.

Power and alpha estimation

- The power was obtained as the percentage of significant results over 10,000 iterations.

RESULTS

Partial level

Marginal level

mRS before the treatment effect addition

mRS after adding the treatment effect

OR = 1.20

	0	1	2	3	4	5	6
0	16.0	12.2	14.5	9.8	5.3	4.1	3.1
1	17.6	15.5	17.9	13.8	8.9	6.8	5.5
2	17.3	16.6	18.1	16.0	12.3	9.6	8.7
3	18.1	18.7	18.6	19.1	18.1	14.8	15.2
4	18.8	21.5	18.7	23.5	28.1	27.2	30.1
5	4.1	5.0	4.0	5.5	8.0	9.4	9.9
6	8.2	10.5	8.1	12.4	19.5	28.1	27.6

	0	1	2	3	4	5	6
0	100.0	7.7	1.1	0.2	0.0	0.0	0.0
1	0.0	92.3	12.4	2.0	0.3	0.1	0.0
2	0.0	0.0	86.5	13.7	1.8	0.5	0.1
3	0.0	0.0	0.0	84.2	10.8	3.2	0.4
4	0.0	0.0	0.0	0.0	87.2	25.2	2.9
5	0.0	0.0	0.0	0.0	0.0	71.0	7.9
6	0.0	0.0	0.0	0.0	0.0	0.0	88.8

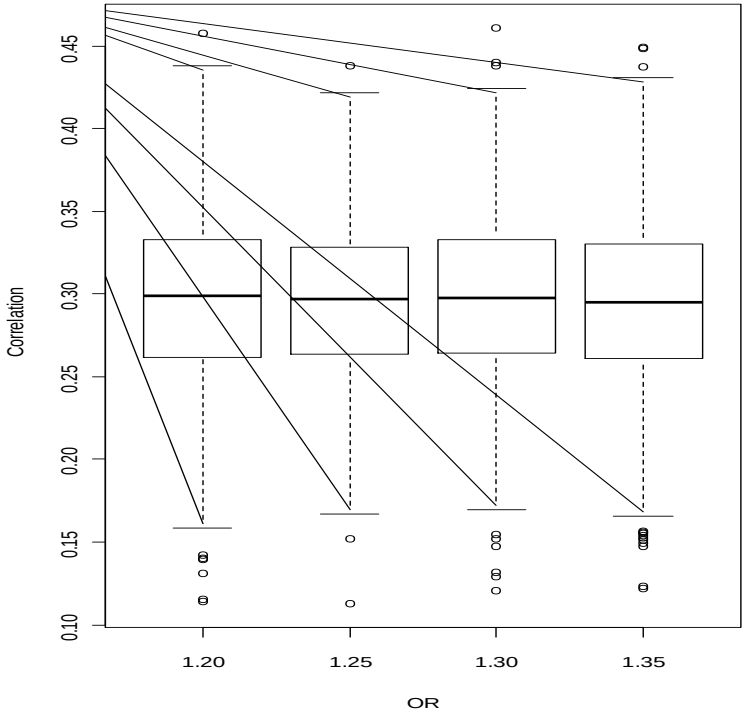
OR = 1.35

	0	1	2	3	4	5	6
0	17.3	13.4	16.0	10.8	5.9	4.6	3.4
1	18.3	16.3	18.7	14.7	9.5	7.4	6.0
2	17.7	16.9	18.3	16.4	13.0	10.2	9.4
3	17.7	18.5	18.2	19.1	18.5	15.0	16.0
4	17.9	20.7	17.6	22.5	27.7	27.6	30.1
5	3.7	4.6	3.7	5.2	7.6	9.1	9.6
6	7.3	9.5	7.4	11.3	17.9	26.0	25.4

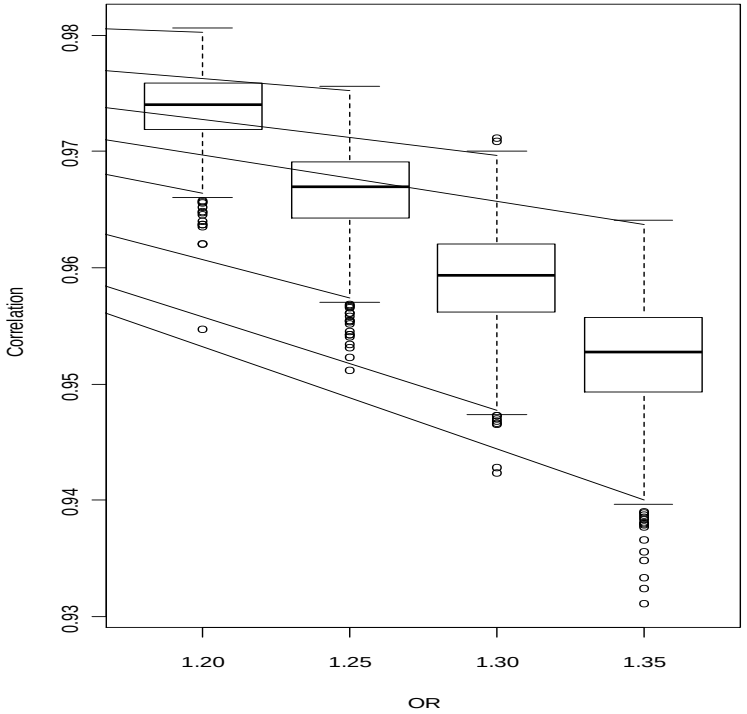
	0	1	2	3	4	5	6
0	100.0	12.0	2.5	0.6	0.1	0.1	0.0
1	0.0	88.0	17.8	4.4	0.9	0.4	0.1
2	0.0	0.0	79.7	19.2	4.0	1.6	0.3
3	0.0	0.0	0.0	75.8	15.5	6.5	1.2
4	0.0	0.0	0.0	0.0	79.5	32.8	6.0
5	0.0	0.0	0.0	0.0	0.0	58.7	10.5
6	0.0	0.0	0.0	0.0	0.0	0.0	81.9

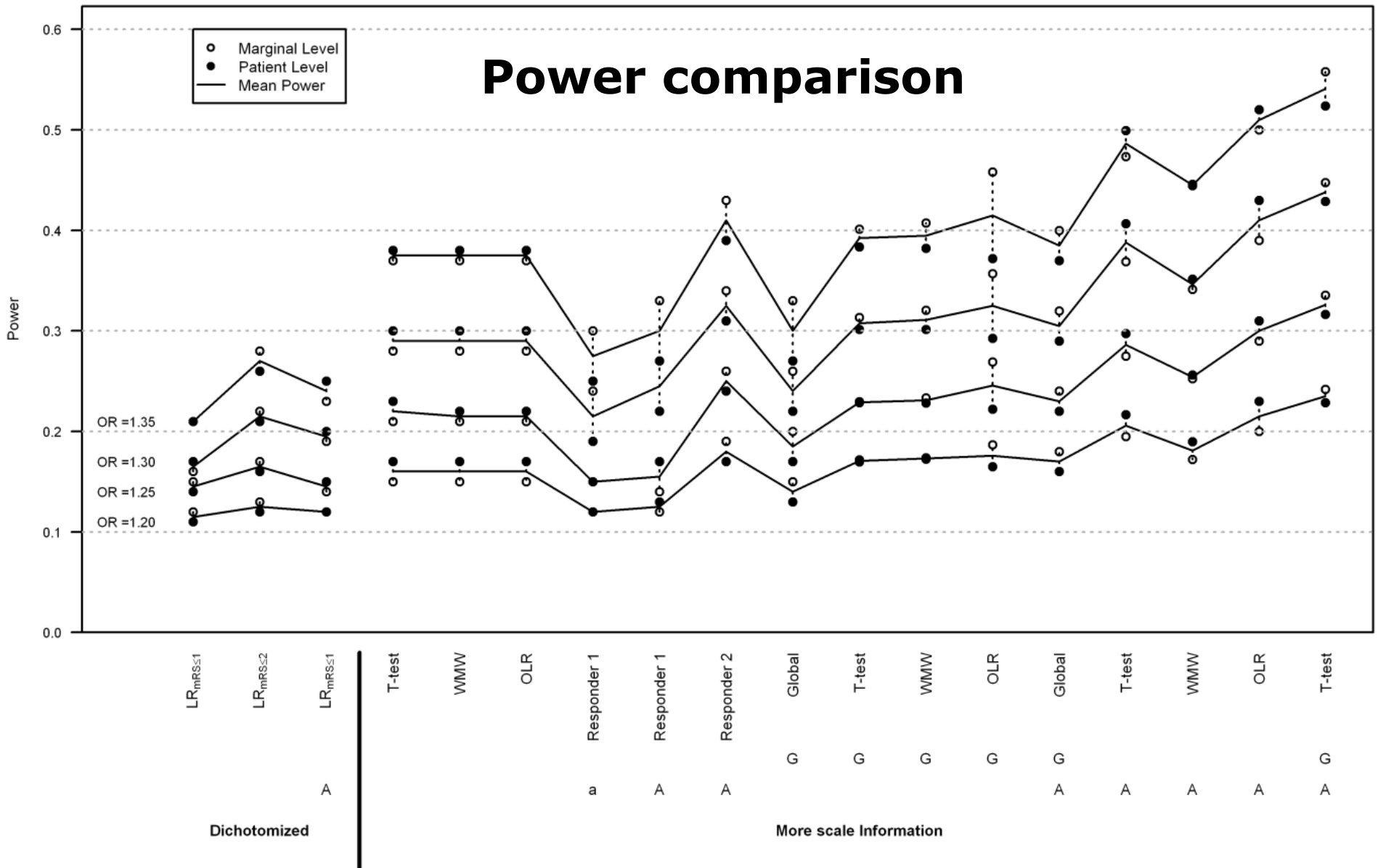
Correlations between the original and simulated outcomes

Partial level

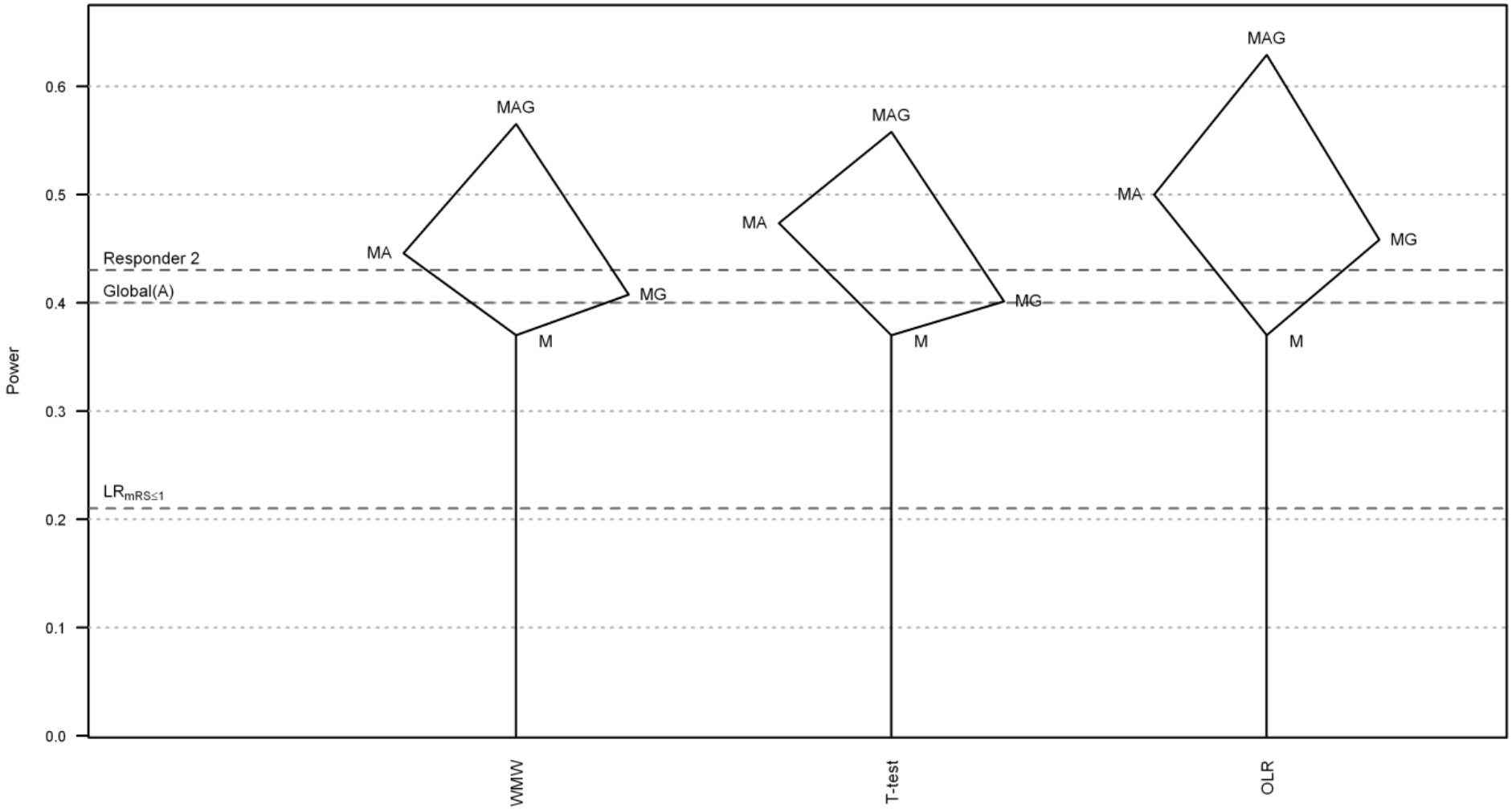


Marginal level




Power comparison
Marginal Level
Patient Level
Mean Power
Power
0.0
0.1
0.2
0.3
0.4
0.5
0.6
OR =1.35
OR =1.30
OR =1.25
OR =1.20
LR mRS≤1
LR mRS≤2
LR mRS≤1
T-test
WMW
OLR
Responder 1
Responder 1
Responder 2
Global
T-test
WMW
OLR
Global
T-test
WMW
OLR
T-test
G
G
G
G
G
G
A
a
A
A
A
A
A
A
Dichotomized
More scale Information

Power comparison



Marginal level scenario

CONCLUSIONS

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LIMITATIONS

Conclusions

- In Stroke trials, the analysis of ordinal scales might be improved by
  - taking into account the ordinal characteristic of the scales,
  - adjusting by prognostic variables,
  - incorporating information of other scales.

- Need to define a **formal** method to incorporate these three factors

Thanks!!