

# **Efficient analysis of ordinal functional outcome scales**

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# Outline of presentation

- **Functional outcome scales**
- **Ordinal analysis**
- **Case study: SCAST**
- **Results**
- **Points to consider**
- **Conclusions**

# **Functional outcome scales**

**Many phase III stroke trials use a functional outcome scale as their primary outcome measure.**

**Examples:**

- **The modified Rankin Scale (mRS)**
- **The Glasgow Outcome Scale (GOS)**

# **modified Rankin Scale (mRS)**

**(van Swieten et al 1988)**

- 0 - No symptoms**
- 1 - Symptoms, but no significant disability**
- 2 - Slight disability**
- 3 - Moderate disability**
- 4 - Moderately severe disability**
- 5 - Severe disability**
- 6 - Dead**

# **Glasgow Outcome Scale (GOS)**

**(Jennett and Bond, 1975)**

- **Good recovery**
- **Moderate disability**
- **Severe disability**
- **Vegetative state**
- **Dead**

# **Analysis of ordinal outcome scales**

- **Conventional dichotomy**
- **Proportional odds model / ordinal regression**
- **Sliding dichotomy**

# Conventional dichotomy

- **mRS: ‘Dead or dependent’ *versus* ‘Independent’**  
**[2-6 versus 0-1 OR 3-6 versus 0-2]**
- **GOS: ‘Unfavourable’ versus ‘Favourable’**  
**[Dead/Vegetative state/Severe disability *versus***  
**Moderate disability/Good recovery]**
- **Discards relevant information, so statistically inefficient**
- **Not in accord with clinical practice**

# Proportional odds model

- **Assume that the odds ratio for a ‘worse’ outcome versus a ‘better’ outcome on treatment is the same for all possible splits of the ordinal scale**
- **Derive a pooled estimate of this ‘common odds ratio’**



# Sliding dichotomy

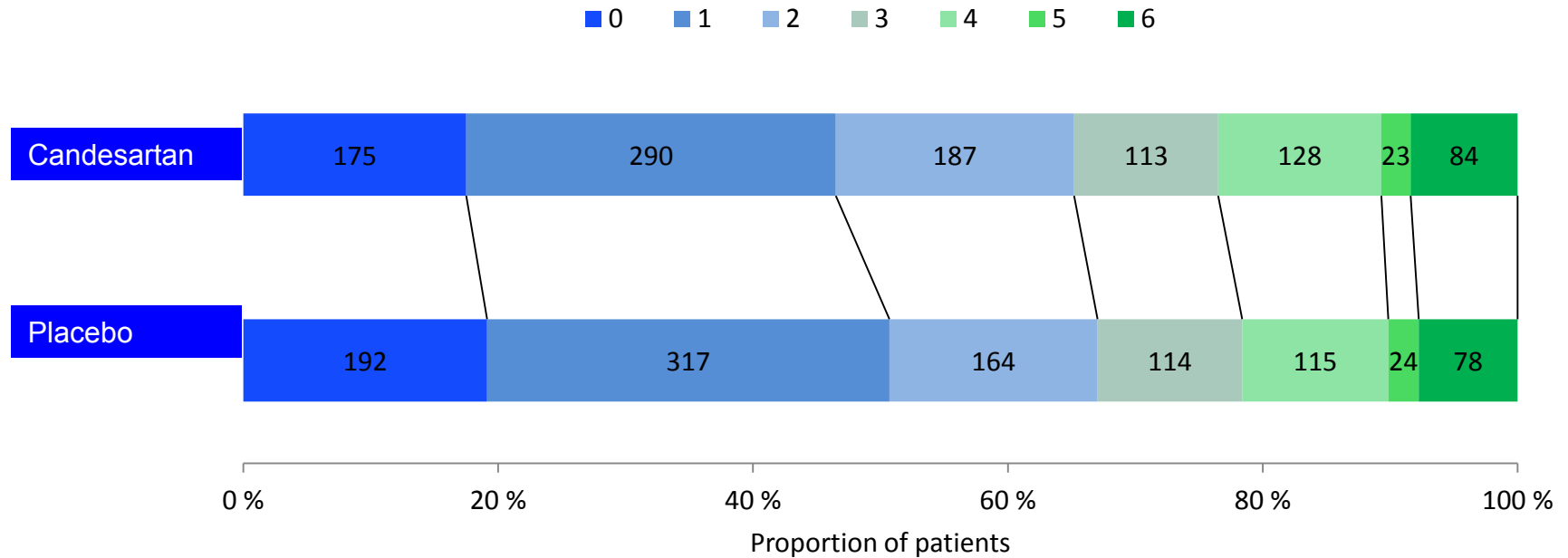
- **Still collapse the ordinal scale to give a binary outcome**
- **BUT, choose the point of dichotomisation according to each individual patient's baseline prognosis**
- **Derive a pooled estimate of the odds ratio for a 'better than expected outcome' on treatment**

## **SCAST (*Lancet* 2011; 377:741-750)**

- **Scandinavian Candesartan Acute Stroke Trial**
- **A trial of careful blood pressure reduction in patients with acute stroke and raised blood pressure**
- **2029 patients randomised to candesartan or placebo in 146 north European centres**
- **2004 patients were assessed for mRS at 6 month follow-up**

# SCAST: mRS at 6 months

[0 – no symptoms to 6 – dead]



# Dichotomous analysis of the mRS

<b>Better Outcome</b>	<b>Worse Outcome</b>	<b>Odds Ratio</b>	<b>95% CI</b>
<b>mRS 0</b>	<b>mRS 1-6</b>	<b>1.11</b>	<b>0.89 to 1.40</b>
<b>mRS 0-1</b>	<b>mRS 2-6</b>	<b>1.18</b>	<b>0.99 to 1.41</b>
<b>mRS 0-2</b>	<b>mRS 3-6</b>	<b>1.09</b>	<b>0.90 to 1.31</b>
<b>mRS 0-3</b>	<b>mRS 4-6</b>	<b>1.11</b>	<b>0.90 to 1.37</b>
<b>mRS 0-4</b>	<b>mRS 5-6</b>	<b>1.06</b>	<b>0.80 to 1.41</b>
<b>mRS 0-5</b>	<b>mRS 6</b>	<b>1.09</b>	<b>0.79 to 1.50</b>

# Dichotomous analysis of the mRS (unadjusted)

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mRS 0-3	mRS 4-6	1.11	0.90 to 1.37
mRS 0-4	mRS 5-6	1.06	0.80 to 1.41
mRS 0-5	mRS 6	1.09	0.79 to 1.50

**Common odds ratio: 1.13 (95% CI 0.97 to 1.32)**

# Fitting the sliding dichotomy (i)

## Prognostic model: Scandinavian Stroke Scale at baseline (pre-randomisation)

- **Consciousness – 0 to 6**
- **Eye movement – 0 to 4**
- **Arm, motor power – 0 to 6**
- **Hand, motor power – 0 to 6**
- **Leg, motor power – 0 to 6**
- **Orientation – 0 to 6**
- **Speech – 0 to 10**
- **Facial palsy – 0 to 2**
- **Gait – 0 to 12**

# Fitting the sliding dichotomy (ii)

## Split the SSS into thirds:

- 0 to 36 (n=656) [poor prognosis]
- 37 to 48 (n=690) [intermediate prognosis]
- 49 to 58 (n=658) [good prognosis]

# Fitting the sliding dichotomy (iii)

		Good	1	2	3	4	5	Dead
Poor prognosis	Placebo	16	41	55	59	81	20	57
	Candesartan	14	44	58	51	82	18	60
Intermediate prognosis	Placebo	53	134	70	43	28	3	13
	Candesartan	43	115	90	43	35	4	16
Good prognosis	Placebo	123	142	39	12	6	1	8
	Candesartan	118	131	39	19	11	1	8

Unfavourable outcomes: Placebo 523/1004 (52%)

Candesartan 557/1000 (56%)



# Summary of results

	Adjusted odds ratio	95% CI	SE of $\log_e(\text{OR})$
Conventional dichotomy	1.12	0.90 to 1.41	0.116
Sliding dichotomy	1.15	0.97 to 1.38	0.090
Proportional odds model	1.17	1.00 to 1.38	0.081

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Effective sample size for PO relative to CD increases by a factor of  $(0.116/0.081)^2 = 2.05$

# Fitting the sliding dichotomy (iv)

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# Points to consider

- **Is the outcome scale actually ordinal?**
- **What if the treatment effect does not comprise a simple ‘shift’ along the outcome scale?**
- **What if there is an interaction between treatment effect and prognosis?**
- **Are there useful measures of clinical impact, analogous to ‘number needed to treat’?**
- **Can ordinal approaches be used in the meta analysis of published trials?**

# Conclusions

- In the case of SCAST, ordinal analysis of the mRS using the proportional odds model more than doubled the effective sample size
- Use of the sliding dichotomy also resulted in substantial efficiency gains
- Similar gains have been observed in other phase III trials, including CRASH and IST-3
- These findings in specific trials are consistent with a large body of methodological evidence based on data from stroke trials (see the work of the OAST Collaboration) and head injury trials (see McHugh *et al*, *Clinical Trials*, 2010;7:44-57)