Optimising the analysis of vascular prevention trials: re-assessment of the TARDIS trial, the first prevention trial to adopt an ordinal primary outcome measure.

SUPPLEMENTARY APPENDIX

Writing Committee

Lisa J Woodhouse;[1] Alan A Montgomery;[2] Stuart Pocock;[3] Marilyn James;[2] Anna Ranta;[4] and Philip M Bath;[1, 5] for the TARDIS Investigators

1. Stroke Trials Unit, Mental Health & Clinical Neurosciences, University of Nottingham, D Floor South Block, Queen's Medical Centre, Nottingham NG7 2UH, UK
2. Nottingham Clinical Trials Unit, University of Nottingham, Queen's Medical Centre, Derby Road, Nottingham NG7 2UH, UK
3. London School of Hygiene & Tropical Medicine, Keppel St., London WC1E 7HT, UK
4. Department of Medicine, University of Otago Wellington, Wellington 6242, New Zealand
5. Stroke, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham NG7 2UH, UK

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Table 1. Overview of statistical analysis methods

Analysis method	Outcome type	Statistical assumptions	Advantages	Disadvantages
Binary logistic regression (BLR)	Binary	• No assumptions made about explanatory variables	• Can adjust for covariates	• Large number of observations required
Cox proportional hazards (CPH)	Binary	• Proportionality of hazards over time • Censoring of observations is unrelated to prognosis	• Can adjust for covariates	• If assumptions of the model not met then subsequent analyses and risk estimates will possibly be biased
Chi-square (χ^2) (CS)	Binary and ordered categorical	• Chi-Square – Total count is >40 or total count is 20-40 and the expected value of each exposure-outcome category is >5	• Simple to implement	• Cannot adjust for covariates
Cochran-Armitage trend test (CAT)	Ordered categorical	• Similar to the Chi-square test but it takes into account the ordering across categories	• Easy to interpret	• Cannot adjust for covariates
Ordinal logistic regression (OLR)	Ordered categorical	• Response is ordinal • Proportionality of odds	• Can adjust for covariates	• If assumptions of the model not met then subsequent analyses and odds estimates will possibly be biased
Mann-Whitney U test (MWU)	Ordered categorical	• Non-parametric test • Response is ordinal / continuous • Observations from both groups are independent of one another	• Easy to interpret	• Cannot adjust for covariates – there are extensions of this method, which allow for adjustment (34-36)
Median test (MT)	Ordered categorical	• Non-parametric test • Considers the position of each observation relative to the overall median.	• Easy to interpret	• Cannot adjust for covariates • Inefficient (low power) to detect differences if sample size is large.
t-test	Continuous (used on the ordered categorical)	• Homogeneity of variances	• Easy to interpret	• Cannot adjust for covariates
Multiple linear regression (MLR)	Continuous (used on the ordered categorical)	• Linear relationship • Homogeneity of variances • No or little multicollinearity	• Can adjust for covariates	• Assumes linear relationship • Sensitive to outliers
Win Ratio test Wins/losses version (WR)	Combination of multiple outcomes	• Accounts for clinical priorities of endpoints	• Prioritises the most severe outcome • Useful for composite outcomes • Extensions of this approach allow for covariate adjustment • Easy to interpret	• Doesn't use the precise times from randomisation to event occurrence
Bootstrapping (BS)	Ordered categorical	• None	• No assumptions made about the distribution of the data	• Cannot adjust for covariates • Computationally intensive • Doesn't provide a meaningful point estimate

Table 2. Example analysis process – based on 4-level Event outcome analysis process (fatal event/ severe event/ minor event/ no event).

1. For each of the participants with available data regarding the event and severity (e.g., fatal, non-fatal severe, non-fatal minor, no event) the following outcomes were created:

    a. **Ordinal 4-level**– analysed using the following approaches: Unadjusted – ordinal logistic regression, Mann-Whitney U test, Cochran-Armitage trend test, Median test, Chi-Square test, t-test, and bootstrapping of the mean rank; Adjusted – ordinal logistic regression and multiple linear regression.
    b. **Binary (any event/no event)** – analysed using the following approaches: Unadjusted – Chi-Square test, Cox Proportional hazards (incorporating time to first event); Adjusted – binary logistic regression and Cox proportional hazards (incorporating time to first event)
    c. **Binary (fatal event/ no fatal event)** – analysed using Chi-Square test and used for the Win ratio test
    d. **Binary (severe event/ no severe event)** – for use in the Win ratio test only
    e. **Binary (minor event/ no minor event)** – for use in Win ratio test only

2. All of the tests are performed on the corresponding outcome(s) and the p-values are extracted to a new dataset, e.g.

Analysis	Chi-Square (Fatal)	Chi-Square (Binary)	Adjusted BLR	Adjusted CPH	Adjusted OLR	Adjusted MLR	Un-adjusted CPH	C-A trend test	Chi-Square (Ordinal)	Un-adjusted OLR	t-test	Mann-Whitney U	Median test	Boot-strapping	Win ratio
Event 4l	0.91	0.0074	0.0052	0.0039	0.0011	0.0027	0.0049	0.0031	0.43	0.0014	0.0030	0.0013	0.0017	0.0037	0.024

3. Then each of the p-values is ranked 1 to 15, from smallest to largest, e.g.

Analysis	Chi-Square (Fatal)	Chi-Square (Binary)	Adjusted BLR	Adjusted CPH	Adjusted OLR	Adjusted MLR	Un-adjusted CPH	C-A trend test	Chi-Square (Ordinal)	Un-adjusted OLR	t-test	Mann-Whitney U	Median test	Boot-strapping	Win ratio
Event 4l	15	12	11	9	1	5	10	7	14	3	6	2	4	8	13

4. This process, with adjustment depending on number of levels, is performed for each ordinal outcome in Table 1.

Analysis	Chi-Square (Fatal)	Chi-Square (Binary)	Adjusted BLR	Adjusted CPH	Adjusted OLR	Adjusted MLR	Un-adjusted CPH	C-A trend test	Chi-Square (Ordinal)	Un-adjusted OLR	t-test	Mann-Whitney U	Median test	Boot-strapping	Win ratio
Event 4l	15	12	11	9	1	5	10	7	14	3	6	2	4	8	13
Event Xl	15	13	10	11	3	6	12	5	14	2	7	1	8	9	4
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Table 3. P-values of tests for each outcome in all participants.

Outcome	N	Levels	MWU	OLR	Median	WR	Adj. OLR	Ord. Chi	CAT	t-test	BS	Adj. MLR	Fatal Chi*	Adj. CPH*	CPH*	Adj. BLR*	Bin Chi*
Stroke, including TIA	3070	4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
(Primary outcome)		6	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		9	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Stroke	3070	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		8	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
MI	3070	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
MI, including angina	3070	4†	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5†	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5‡	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		6†	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		6‡	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		7‡	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Bleeding event	3072	3	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	~	++++	++++	++++	++++
		4	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	~	++++	++++	++++	++++
		5	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	~	++++	++++	++++	++++
Cardiac event	3070	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
VTE	3070	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
SAE	3074	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
MACE	3070	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	++++	~	~	~	~	~	~	~	~	~	~	~	~

*Tests performed on binary cuts of ordinal outcomes. †Includes a composite of stable and unstable angina as a level. ‡Includes stable and unstable angina as separate levels.

Adj.: adjusted; Bin Chi: Binary Chi-square test; BLR: binary logistic regression; BS: bootstrapping; CAT: Cochran-Armitage trend test; CPH: Cox proportional hazards; Fatal Chi: Chi-square test performed on binary Fatal event/no event outcome; MACE: Major Adverse

Cardiovascular event; Median: median test; MI: myocardial infarction; MLR: multiple linear regression; MWU: Mann-Whitney U test; OLR: ordinal logistic regression; Ord. Chi: Ordinal Chi-square test; SAE: Serious Adverse Event; VTE: Venous thromboembolism; WR: win ratio test.

Key: p >0.1 (~), 0.05-0.09 (+), 0.01-0.049 (++), 0.001-0.0099 (+++), <0.001 (++++).

Table 4. P-values of tests for each outcome in Minor stroke/ TIA participants recruited within 24 hours.

Outcome	N	Levels	MWU	OLR	Median	WR	Adj. OLR	Ord. Chi	CAT	t-test	BS	Adj. MLR	Fatal Chi*	Adj. CPH*	CPH*	Adj. BLR*	Bin Chi*
Stroke, including TIA	755	4	++	++	++	++	++	+	++	++	++	+	~	~	~	~	~
		5	++	++	++	++	++	+	++	++	++	+	~	~	~	~	~
(Primary outcome)		6	++	++	++	++	++	~	++	++	++	+	~	~	~	~	~
		9	++	++	++	++	++	~	++	++	++	+	~	~	~	~	~
Stroke	755	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		8	~	~	~	~	~	~	+	+	~	~	~	~	~	~	~
MI	755	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
MI, including angina	755	4†	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5†	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5‡	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		6†	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		6‡	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		7‡	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Bleeding event	756	3	++	++	++	++	+++	++	++	++	++	+++	~	+++	++	+++	++
		4	++	++	++	++	+++	~	++	++	++	+++	~	+++	++	+++	++
		5	++	++	++	++	+++	~	++	++	++	++	~	+++	++	+++	++
Cardiac event	755	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
SAE	756	3	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		4	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
		5	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
MACE	755	3	++	++	++	+	++	+	++	++	++	++	~	++	++	++	++
		4	++	++	++	+	++	~	+	+	+	+	~	++	++	++	++
		5	++	++	++++	+	++	+	++	++	++	+	~	++	++	++	++

*Tests performed on binary cuts of ordinal outcomes. †Includes a composite of stable and unstable angina as a level. ‡Includes stable and unstable angina as separate levels.

Adj.: adjusted; Bin Chi: Binary Chi-square test; BLR: binary logistic regression; BS: bootstrapping; CAT: Cochran-Armitage trend test; CPH: Cox proportional hazards; Fatal Chi: Chi-square test performed on binary Fatal event/no event outcome; MACE: Major Adverse Cardiovascular event; Median: median test; MI: myocardial infarction; MLR: multiple linear regression; MWU: Mann-Whitney U test; OLR: ordinal logistic regression; Ord. Chi: Ordinal Chi-square test; SAE: Serious Adverse Event; WR: win ratio test.

Key: p >0.1 (~), 0.05-0.09 (+), 0.01-0.049 (++), 0.001-0.0099 (+++), <0.001 (++++).