Generalized pairwise comparison methods to analyze (non)-hierarchical composite endpoints

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Overview

- Introduction to non-parametric generalized pairwise comparison analysis
- Description of four generalized pairwise comparison methods
- Application to simulations of TAVR UNLOAD study

Introduction to non-parametric generalized pairwise comparison analysis

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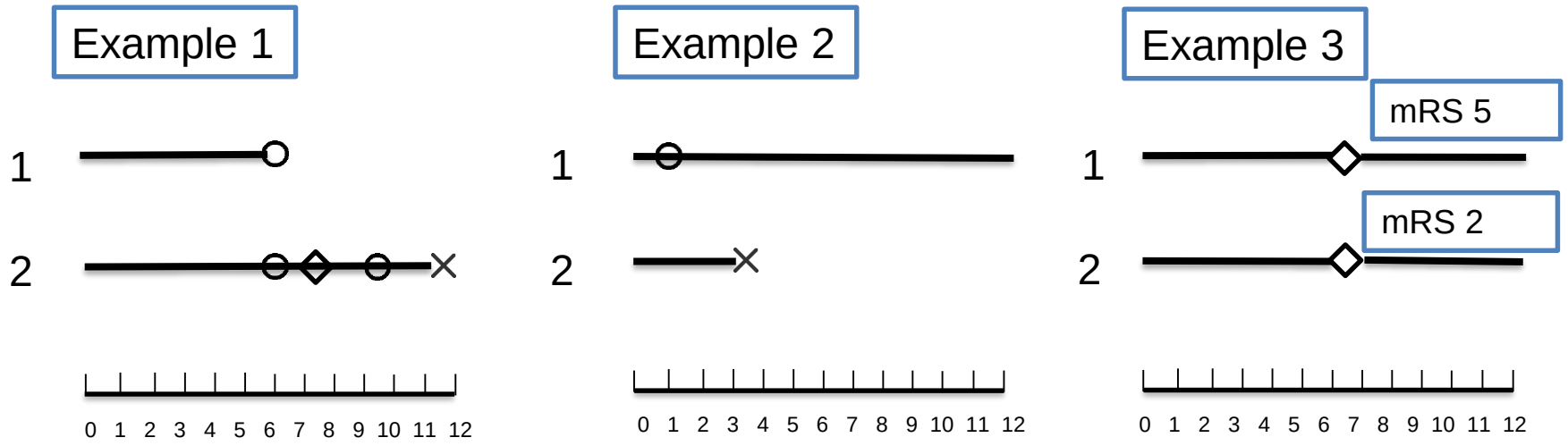
Issues classical composite endpoint analysis

- Time to first event analysis (Logrank or Cox proportional hazard)



X = death; ◇ = stroke ; ○ = hospitalization

mRS = modified Rank Score

Simplest pairwise comparison method

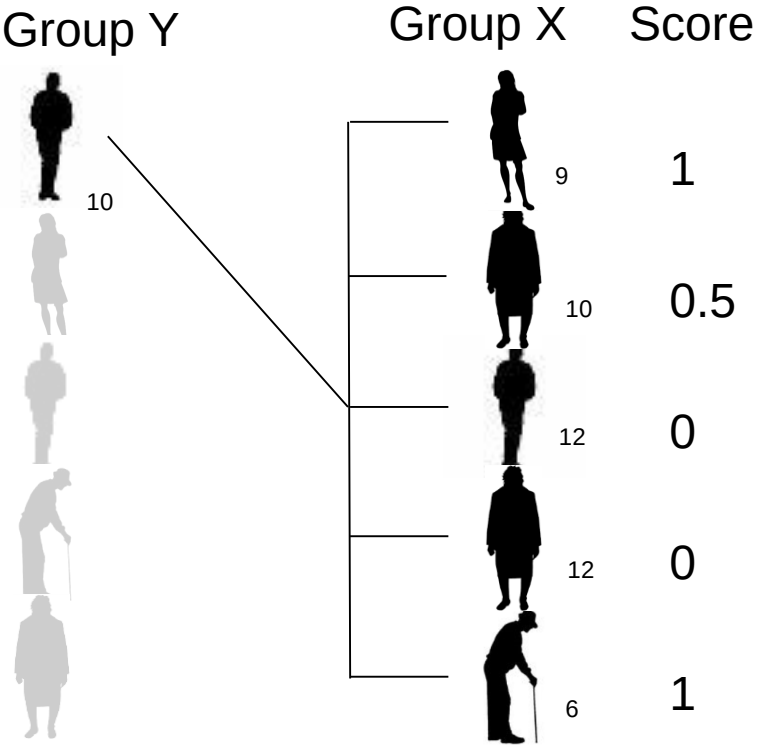
- Mann-Whitney U test

Scoring

1 if Y wins

0 if X wins

0.5 if tie



Summed score: 2.5

Mann et al. *The annals of Math Stat* (1947) 18: 50-60

Simplest pairwise comparison method

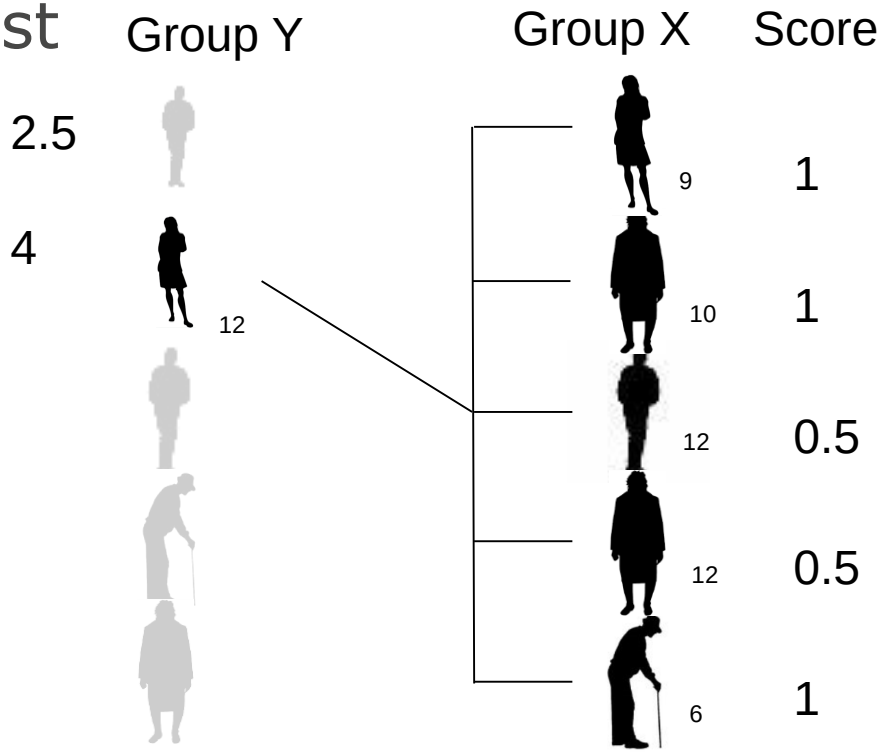
- Mann-Whitney U test

Scoring

1 if Y wins

0 if X wins

0.5 if tie



Summed score: 4

Mann et al. *The annals of Math Stat* (1947) 18: 50-60

Simplest pairwise comparison method

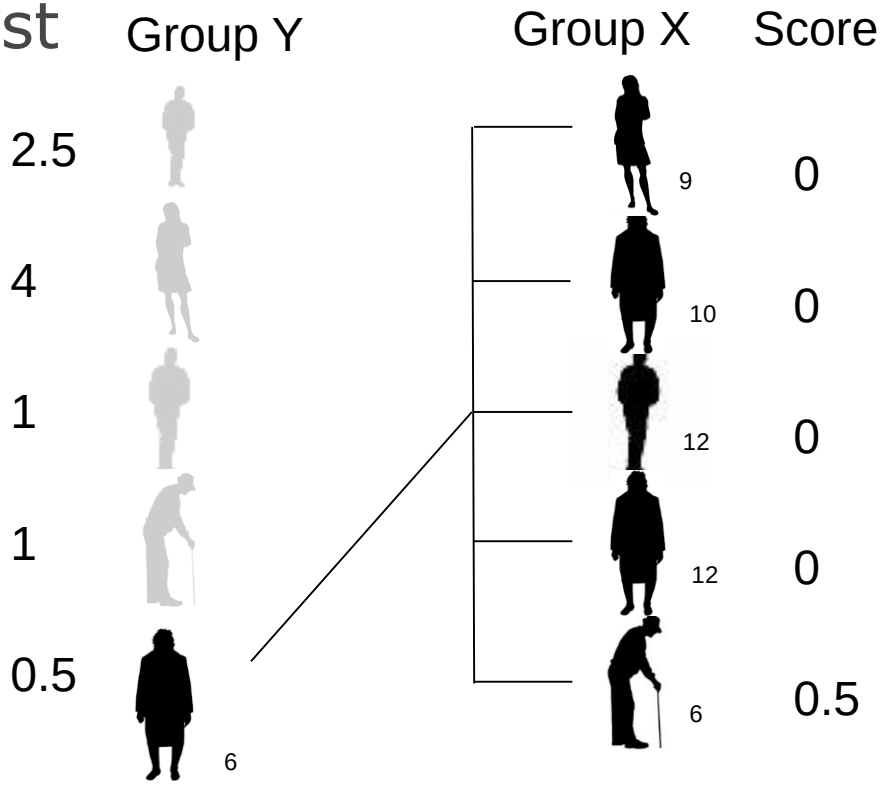
- Mann-Whitney U test

Scoring

1 if Y wins

0 if X wins

0.5 if tie



Statistic U_{XY} : 9.5

Mann et al. *The annals of Math Stat* (1947) 18: 50-60

Gehan generalization to **censored data**

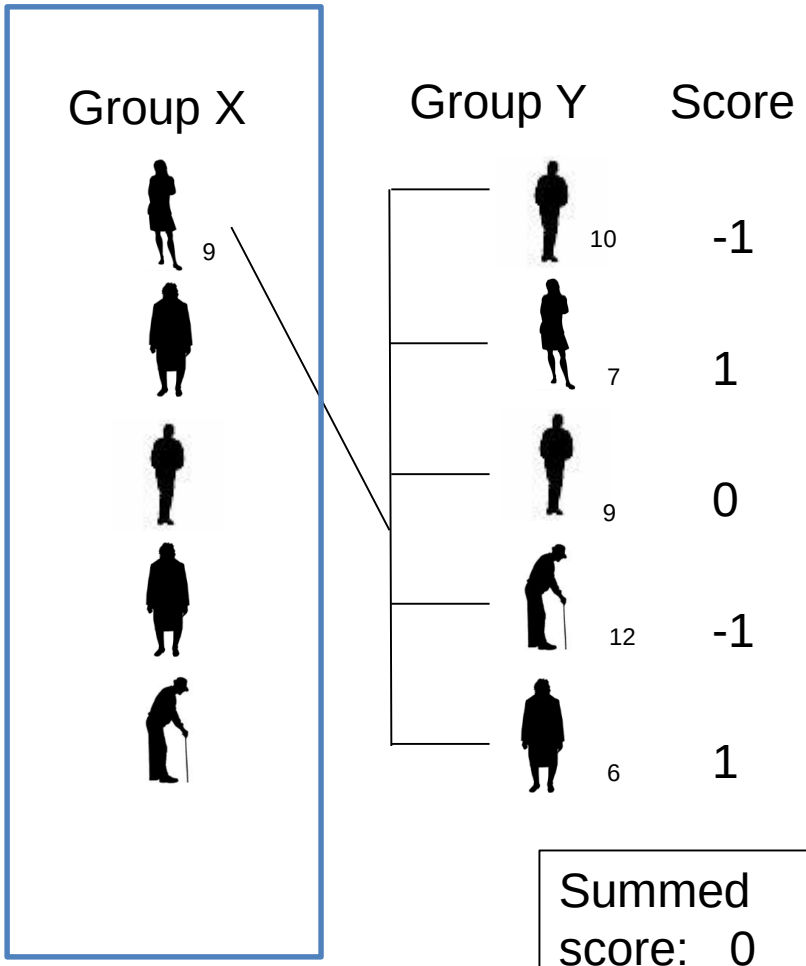
- Score Gehan Test

Scoring

1 if X_i wins

-1 if X_i loses

0 if tie



Repeat and sum only for Group X

Summed score: 0

Gehan. *Biometrika* (1965) 52: 203-223

Gehan generalization to censored data

- Score Gehan Test

Scoring

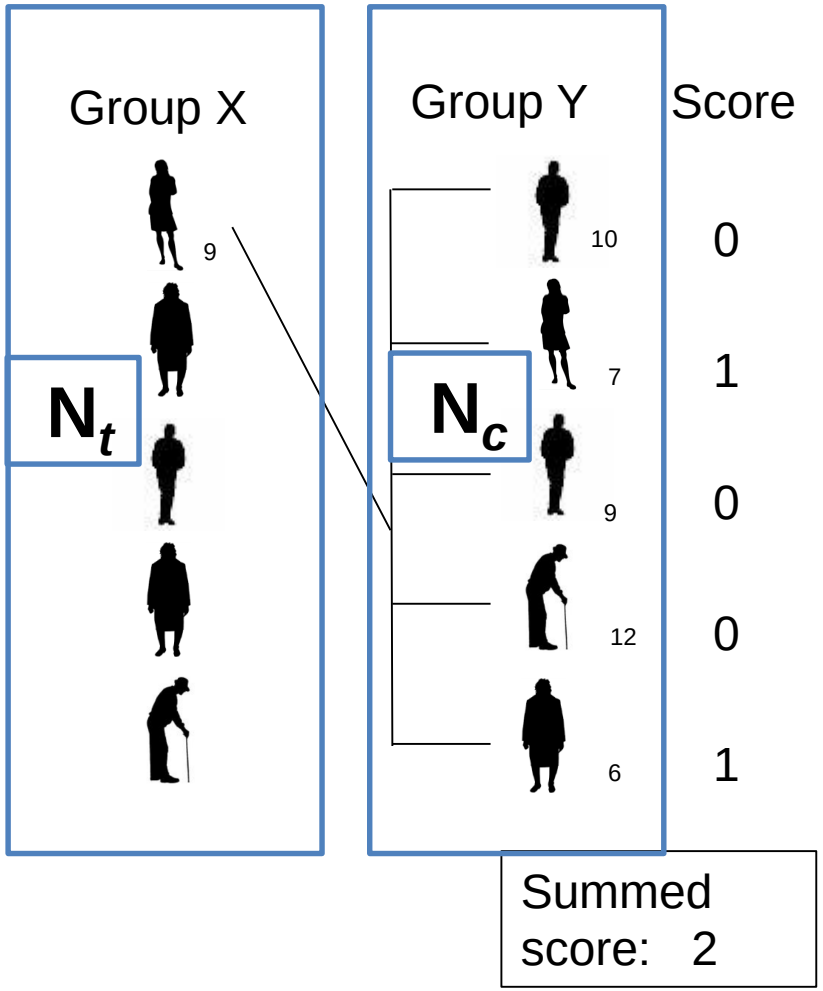
1 if X_i wins

0 else

Scoring

1 if Y_i wins

0 else

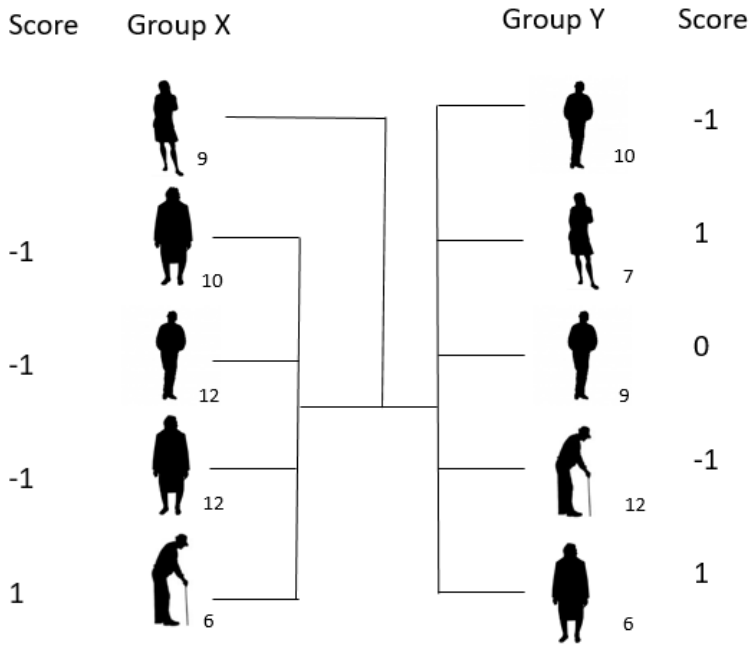


Repeat for Group X and Group Y and substract

Win difference: N_t - N_c

Generalization to censored data

- Score Gehan Test - **Variance**



Permutation distribution

Asymptotically Normal distributed

Description of four Generalized Pairwise Comparison methods

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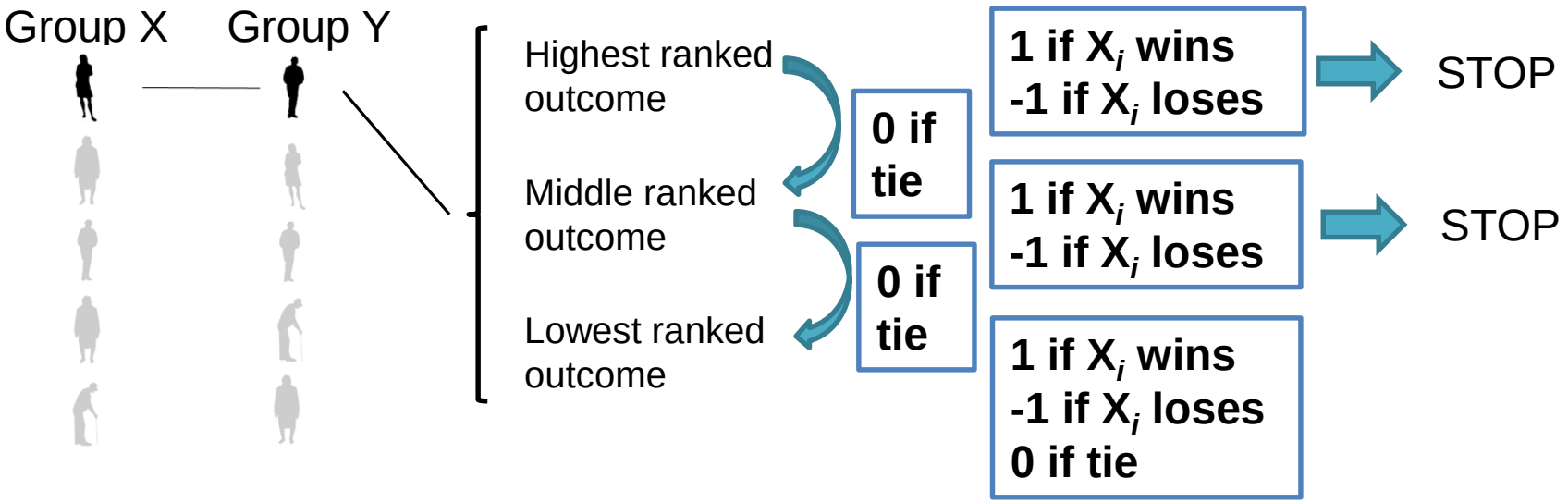
Generalization to **composite endpoints**

1. The **Finkelstein-Schoenfeld test** is a generalization of the **Score Gehan test** for multiple outcomes



Finkelstein et al. *Statist. Med.* (1999) 18: 1341-1354

Generalization to composite endpoints

2. The **Buyse test**

Net benefit : $\frac{N_t - N_c}{nm}$

U-statistic
Asymptotically
Normal distributed

Adapted, since originally defined as a randomization test

Buyse. *Statis Med* (2010) 29. 3245-3257
Ramchandani et al. *Biometrics.* (2016) 72. 926-935

Gehan generalization to censored data

3. The **Unmatched Pocock test**

Scoring

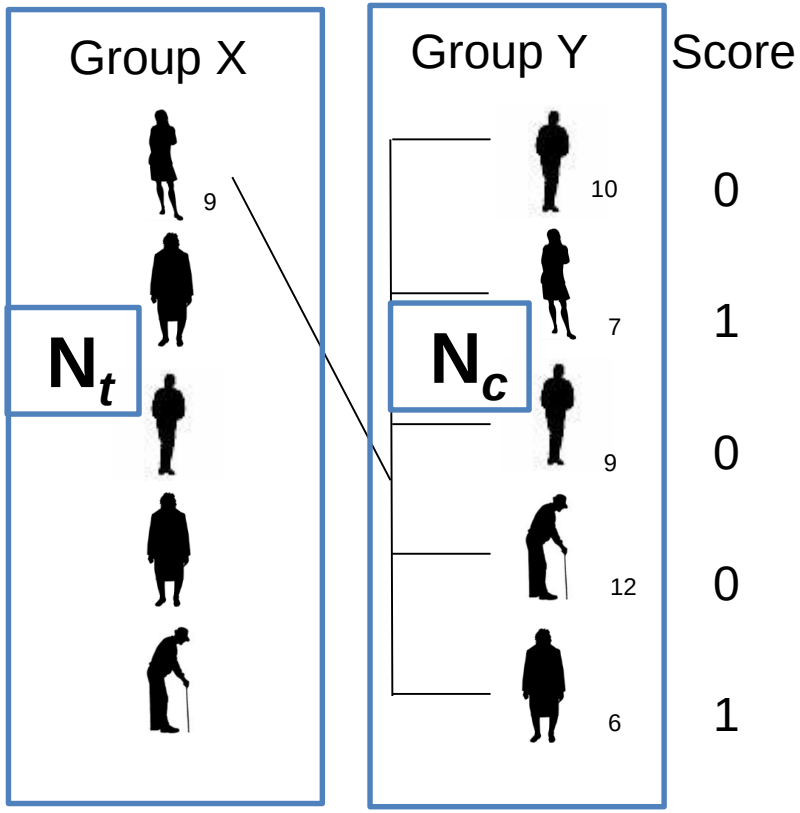
1 if X_i wins

0 if tie

Scoring

1 if Y_i wins

0 if tie



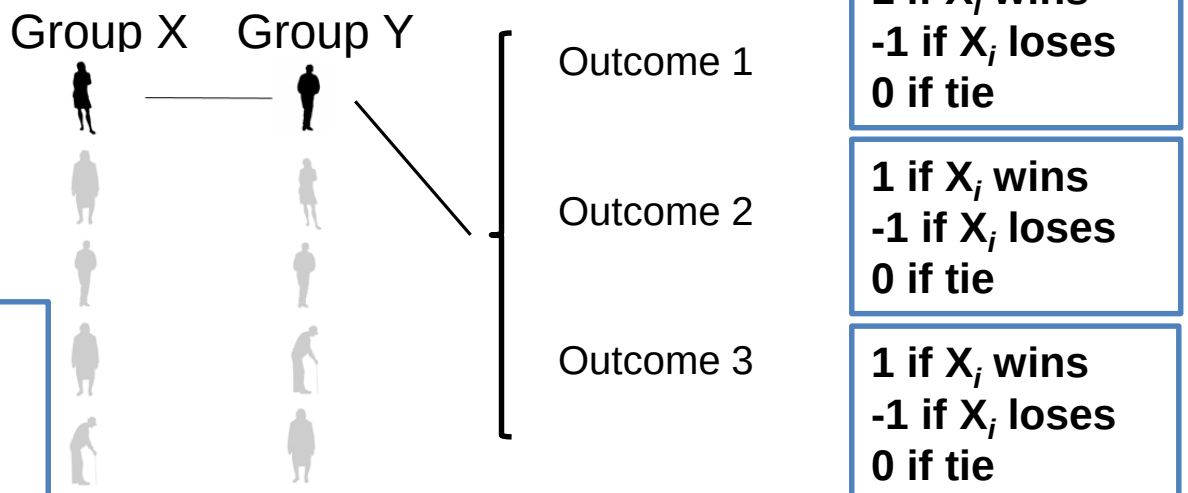
Win Ratio: N_t / N_c

U-statistic
Logarithmic Asymptotically
Normal distributed

Pocock et al. *EHJ* (2012) 33: 176-182
Dong et al. *Pharmac Statist* (2016) 15: 430-437

Generalization to composite endpoints

4. The **Adapted O'Brien test** (non-hierarchical)



Net benefit

U-statistics Asymptotically Normal distributed

O'Brien. Biometrics (1985) 40. 1079-1087
Ramchandani et al. *Biometrics.* (2016) 72. 926-935

Application to simulations of TAVR UNLOAD study

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TAVR UNLOAD – Hierarchical endpoint at 1y

Level	Endpoints	Type
1	Time to Death	In days
2	Time and Severity of disabling stroke	Categorical (mRS 2-5)
3	Frequency of hospitalization and number of days hospitalized	Count
4	Effect on KCCQ (=QoL)	Categorical: • ≥10 points worse • 5-9 points worse • Equal • 5-9 points better • ≥10 points better

Importance of events are taken into account
Multiplicity is taken into account
Severity of events are taken into account

mRS= modified Rankin Score (from 0-6; but 0= no symptoms; 1= no disability and 6= death)
KCCQ=Kansas City Cardiomyopathy Questionnaire; 23 questions; scored 0-100

Simulations

- Compare power to classic logrank test
- 4 scenario's: null scenario, scenario 1-3
- 1000 simulations
- 10, 20 and 50% equal censoring
- Sample size: 600, 400, 300, 250, 200, 100
- Leave levels of hierarchy out

Generalized Pairwise comparisons better powered than logrank

	Scenario 0					Scenario 1					Scenario2					Scenario 3				
Censoring	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L
N=600																				
0%	4.5	4.5	4.5	4.1	4.5	99.9	99.9	99.9	100	75.1	100	100	100	100	53.9	98.6	98.6	98.6	99.8	39.3
20%	3.6	3.6	3.6	3.7	4.9	99.2	99.2	99.2	100	68.1	99.4	99.4	99.4	100	47.6	98.8	98.8	98.7	100	45.3
50%	5.1	5.1	5.0	5.4	4.7	85.3	85.2	85.0	95.8	56.5	80.9	80.8	80.2	91.4	38.1	82.8	82.6	82.6	92.6	39.5
N=400																				
0%	6.0	6.0	5.9	5.7	5.6	99.0	99.0	99.0	99.9	58.9	98.7	98.6	98.6	100	39.3	98.4	98.4	98.4	99.8	37.7
20%	4.4	4.4	4.4	3.9	4.8	94.1	94.0	93.9	99.3	51.1	94.7	94.4	94.4	99.2	33.3	94.9	94.9	94.6	98.3	32.2
50%	5.0	5.0	5.0	5.2	5.3	68.1	67.7	66.8	82.5	38.8	64.8	64.6	63.9	79.7	27.2	62.6	62.7	61.9	76.8	27.2
N=300																				
0%	5.6	5.6	5.6	6.3	5.2	94.7	94.3	94.3	99.1	44.8	95.7	95.7	95.6	99.1	34.4	94.9	94.8	94.8	98.2	30.0
10%	6.0	5.9	5.9	5.6	5.4	92.5	91.8	91.5	98.9	41.4	92.5	92.2	92.2	98.6	26.6	93.0	92.9	92.9	97.3	28.5
20%	4.7	4.7	4.5	4.1	5.4	86.0	85.3	84.9	96.3	38.5	88.6	88.0	87.7	95.8	25.2	86.7	86.0	85.8	95.2	26.3
50%	5.2	5.3	4.9	4.4	6.1	55.9	55.3	54.6	70.8	30.5	53.9	53.6	52.8	66.8	22.4	53.5	53.5	52.5	64.4	20.6
N=250																				
0%	4.5	4.5	4.5	4.5	4.6	91.2	91.2	91.0	98.5	40.8	92.1	91.6	91.4	97.7	28.1	91.7	91.4	91.2	97.4	27.3
10%	6.0	6.0	5.5	5.2	5.2	85.7	85.2	84.9	96.7	35.9	87.9	87.6	87.6	95.7	23.8	89.5	89.2	88.7	94.9	24.9
20%	5.0	4.8	4.7	5.6	4.9	79.0	78.6	78.3	91.8	32.9	83.3	82.8	82.3	93.9	24.7	82.8	82.2	81.6	90.7	23.9
N=200																				
0%	3.8	3.8	3.4	3.5	5.0	83.1	82.6	82.1	95.7	31.0	85.7	85.4	85.0	94.5	22.6	85.0	84.8	84.1	93.0	20.8
10%	4.8	4.6	4.6	4.0	5.1	75.3	74.6	74.2	91.1	29.2	79.2	78.5	77.6	90.9	20.7	78.7	78.1	77.6	89.4	19.7
20%	6.4	6.4	5.8	5.0	5.5	69.5	68.9	68.1	86.5	26.1	73.1	72.3	71.8	86.8	21.3	71.3	70.7	70.2	82.5	17.4
N=100																				
0%	6.0	5.9	5.3	5.5	6.3	54.7	53.2	52.2	69.7	17.8	56.0	54.9	52.9	69.0	14.7	57.4	56.2	55.1	68.3	14.0

Little difference between hierarchical tests

	Scenario 0					Scenario 1					Scenario2					Scenario 3				
Censoring	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L
N=600																				
0%	4.5	4.5	4.5	4.1	4.5	99.9	99.9	99.9	100	75.1	100	100	100	100	53.9	98.6	98.6	98.6	99.8	39.3
20%	3.6	3.6	3.6	3.7	4.9	99.2	99.2	99.2	100	68.1	99.4	99.4	99.4	100	47.6	98.8	98.8	98.7	100	45.3
50%	5.1	5.1	5.0	5.4	4.7	85.3	85.2	85.0	95.8	56.5	80.9	80.8	80.2	91.4	38.1	82.8	82.6	82.6	92.6	39.5
N=400																				
0%	6.0	6.0	5.9	5.7	5.6	99.0	99.0	99.0	99.9	58.9	98.7	98.6	98.6	100	39.3	98.4	98.4	98.4	99.8	37.7
20%	4.4	4.4	4.4	3.9	4.8	94.1	94.0	93.9	99.3	51.1	94.7	94.4	94.4	99.2	33.3	94.9	94.9	94.6	98.3	32.2
50%	5.0	5.0	5.0	5.2	5.3	68.1	67.7	66.8	82.5	38.8	64.8	64.6	63.9	79.7	27.2	62.6	62.7	61.9	76.8	27.2
N=300																				
0%	5.6	5.6	5.6	6.3	5.2	94.7	94.3	94.3	99.1	44.8	95.7	95.7	95.6	99.1	34.4	94.9	94.8	94.8	98.2	30.0
10%	6.0	5.9	5.9	5.6	5.4	92.5	91.8	91.5	98.9	41.4	92.5	92.2	92.2	98.6	26.6	93.0	92.9	92.9	97.3	28.5
20%	4.7	4.7	4.5	4.1	5.4	86.0	85.3	84.9	96.3	38.5	88.6	88.0	87.7	95.8	25.2	86.7	86.0	85.8	95.2	26.3
50%	5.2	5.3	4.9	4.4	6.1	55.9	55.3	54.6	70.8	30.5	53.9	53.6	52.8	66.8	22.4	53.5	53.5	52.5	64.4	20.6
N=250																				
0%	4.5	4.5	4.5	4.5	4.6	91.2	91.2	91.0	98.5	40.8	92.1	91.6	91.4	97.7	28.1	91.7	91.4	91.2	97.4	27.3
10%	6.0	6.0	5.5	5.2	5.2	85.7	85.2	84.9	96.7	35.9	87.9	87.6	87.6	95.7	23.8	89.5	89.2	88.7	94.9	24.9
20%	5.0	4.8	4.7	5.6	4.9	79.0	78.6	78.3	91.8	32.9	83.3	82.8	82.3	93.9	24.7	82.8	82.2	81.6	90.7	23.9
N=200																				
0%	3.8	3.8	3.4	3.5	5.0	83.1	82.6	82.1	95.7	31.0	85.7	85.4	85.0	94.5	22.6	85.0	84.8	84.1	93.0	20.8
10%	4.8	4.6	4.6	4.0	5.1	75.3	74.6	74.2	91.1	29.2	79.2	78.5	77.6	90.9	20.7	78.7	78.1	77.6	89.4	19.7
20%	6.4	6.4	5.8	5.0	5.5	69.5	68.9	68.1	86.5	26.1	73.1	72.3	71.8	86.8	21.3	71.3	70.7	70.2	82.5	17.4
N=100																				
0%	6.0	5.9	5.3	5.5	6.3	54.7	53.2	52.2	69.7	17.8	56.0	54.9	52.9	69.0	14.7	57.4	56.2	55.1	68.3	14.0

O'Brien better powered than hierarchical

	Scenario 0					Scenario 1					Scenario2					Scenario 3				
Censoring	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L	S_{FS}	U_{WR}	U_B	U_O	χ^2_L
N=600																				
0%	4.5	4.5	4.5	4.1	4.5	99.9	99.9	99.9	100	75.1	100	100	100	100	53.9	98.6	98.6	98.6	99.8	39.3
20%	3.6	3.6	3.6	3.7	4.9	99.2	99.2	99.2	100	68.1	99.4	99.4	99.4	100	47.6	98.8	98.8	98.7	100	45.3
50%	5.1	5.1	5.0	5.4	4.7	85.3	85.2	85.0	95.8	56.5	80.9	80.8	80.2	91.4	38.1	82.8	82.6	82.6	92.6	39.5
N=400																				
0%	6.0	6.0	5.9	5.7	5.6	99.0	99.0	99.0	99.9	58.9	98.7	98.6	98.6	100	39.3	98.4	98.4	98.4	99.8	37.7
20%	4.4	4.4	4.4	3.9	4.8	94.1	94.0	93.9	99.3	51.1	94.7	94.4	94.4	99.2	33.3	94.9	94.9	94.6	98.3	32.2
50%	5.0	5.0	5.0	5.2	5.3	68.1	67.7	66.8	82.5	38.8	64.8	64.6	63.9	79.7	27.2	62.6	62.7	61.9	76.8	27.2
N=300																				
0%	5.6	5.6	5.6	6.3	5.2	94.7	94.3	94.3	99.1	44.8	95.7	95.7	95.6	99.1	34.4	94.9	94.8	94.8	98.2	30.0
10%	6.0	5.9	5.9	5.6	5.4	92.5	91.8	91.5	98.9	41.4	92.5	92.2	92.2	98.6	26.6	93.0	92.9	92.9	97.3	28.5
20%	4.7	4.7	4.5	4.1	5.4	86.0	85.3	84.9	96.3	38.5	88.6	88.0	87.7	95.8	25.2	86.7	86.0	85.8	95.2	26.3
50%	5.2	5.3	4.9	4.4	6.1	55.9	55.3	54.6	70.8	30.5	53.9	53.6	52.8	66.8	22.4	53.5	53.5	52.5	64.4	20.6
N=250																				
0%	4.5	4.5	4.5	4.5	4.6	91.2	91.2	91.0	98.5	40.8	92.1	91.6	91.4	97.7	28.1	91.7	91.4	91.2	97.4	27.3
10%	6.0	6.0	5.5	5.2	5.2	85.7	85.2	84.9	96.7	35.9	87.9	87.6	87.6	95.7	23.8	89.5	89.2	88.7	94.9	24.9
20%	5.0	4.8	4.7	5.6	4.9	79.0	78.6	78.3	91.8	32.9	83.3	82.8	82.3	93.9	24.7	82.8	82.2	81.6	90.7	23.9
N=200																				
0%	3.8	3.8	3.4	3.5	5.0	83.1	82.6	82.1	95.7	31.0	85.7	85.4	85.0	94.5	22.6	85.0	84.8	84.1	93.0	20.8
10%	4.8	4.6	4.6	4.0	5.1	75.3	74.6	74.2	91.1	29.2	79.2	78.5	77.6	90.9	20.7	78.7	78.1	77.6	89.4	19.7
20%	6.4	6.4	5.8	5.0	5.5	69.5	68.9	68.1	86.5	26.1	73.1	72.3	71.8	86.8	21.3	71.3	70.7	70.2	82.5	17.4
N=100																				
0%	6.0	5.9	5.3	5.5	6.3	54.7	53.2	52.2	69.7	17.8	56.0	54.9	52.9	69.0	14.7	57.4	56.2	55.1	68.3	14.0

No difference time to first event or time to worst event

Omitted component	Scenario 0 S_{FS}	U_{WR}	U_B	U_O	Scenario 1 S_{FS}	U_{WR}	U_B	χ^2_L	Scenario2 S_{FS}	U_{WR}	U_B	χ^2_L	Scenario 3 S_{FS}	U_{WR}	U_B	χ^2_L
N=600																
None	4.5	4.5	4.5	4.1	99.9	99.9	99.9		100	100	100		98.6	98.6	98.6	
Stroke	4.9	4.9	4.9	4.4	100	100	100	75.1	100	100	100	53.9	100	100	100	39.3
Hospitalization	4.9	4.9	4.7	4.8	99.9	99.9	99.9	100	100	100	100	100	99.9	99.9	99.9	100
KCCQ	5.5	5.6	5.5	5.4	68.9	68.9	68.7	74.1	50.3	50.5	49.7	54.5	52.8	52.8	52.5	55.1
Stroke/Hospital	5.3	5.1	5.0	5.0	99.9	99.9	99.9	99.9	100	100	100	100	100	100	100	100
N=400																
None	6.0	6.0	5.9	5.7	99.0	99.0	99.0	99.9	98.7	98.6	98.6	100	98.4	98.4	98.4	99.8
Death	5.1	5.2	5.0	5.7	99.0	98.8	98.9	100	99.5	99.4	99.4	99.9	99.4	99.4	99.4	100
Stroke	5.8	5.8	5.8	5.3	99.0	99.0	99.0	100	99.5	99.5	99.5	100	99.4	99.4	99.4	100
Hospitalization	5.7	5.7	5.7	5.4	99.8	99.8	99.8	99.9	99.8	99.7	99.7	99.9	99.7	99.7	99.7	99.9
KCCQ	5.4	5.4	5.4	5.1	53.1	53.1	52.4	57.7	36.5	36.6	36.1	40.5	36.5	36.8	35.9	39.6
Stroke/Hospital	5.2	5.2	5.1	5.1	99.8	99.8	99.8	99.8	99.7	99.7	99.7	99.7	99.5	99.5	99.5	99.5
N=300																
None	5.6	5.6	5.6	6.3	94.7	94.3	94.3	99.1	95.7	95.7	95.6	99.1	94.9	94.8	94.8	98.2
Death	5.4	5.4	5.4	5.3	96.0	95.9	95.8	99.5	97.5	97.4	97.4	99.8	97.3	97.2	97.1	99.4
Stroke	6.0	6.0	5.9	6.2	96.7	96.5	96.4	99.4	97.6	97.6	97.6	99.7	97.7	97.7	97.6	99.5
Hospitalization	5.4	5.3	5.2	5.2	98.8	98.8	98.7	99.2	98.8	98.8	98.8	99.4	98.6	98.5	98.3	98.9
Stroke/Hospital	6.4	6.4	6.2	6.2	97.7	97.7	97.6	97.6	98.2	98.2	98.2	98.2	98.0	97.9	97.8	97.8
N=200																
None	3.8	3.8	3.4	3.5	83.1	82.6	82.1	95.7	85.7	85.4	85.0	94.5	85.0	84.8	84.1	93.0
Death	6 .0	5.9	5.7	4.8	84.8	84.2	83.7	97.0	88.4	88.1	87.8	95.7	86.3	85.4	85.1	93.3
Stroke	5.6	5.5	5.3	6.0	86.1	85.9	85.5	96.8	87.2	87.1	86.8	95.1	87.6	87.4	87.4	95.1
Hospitalization	4.8	4.8	4.7	4.4	91.0	90.6	90.5	94.0	92.0	91.5	91.2	94.0	91.1	91.0	90.4	93.6
Stroke/Hospital	4.9	4.9	4.2	4.2	90.5	90.2	89.5	89.5	91.9	91.8	90.9	90.9	91.1	90.8	90.6	90.6
N=100																
None	6.0	5.9	5.3	5.5	54.7	53.2	52.2	69.7	56.0	54.9	52.9	69.0	57.4	56.2	55.1	68.3
Stroke	4.4	4.3	3.8	3.5	55.6	55.4	54.1	72.6	62.0	61.4	60.0	73.9	63.3	62.6	60.9	72.3
Hospitalization	3.7	3.6	3.3	3.0	64.6	64.3	61.9	67.2	67.4	66.8	65.2	69.8	66.2	65.9	64.1	68.8
Stroke/Hospital	4.0	4.3	3.2	3.2	64.0	63.3	61.6	61.6	65.0	64.7	62.2	62.2	61.1	60.5	58.6	58.6

If hospitalization is left out, power hierarchical and non-hierarchical test equal

	Scenario 0				Scenario 1				Scenario2				Scenario 3			
Omitted component	S_{FS}	U_{WR}	U_B	U_O	S_{FS}	U_{WR}	U_B	U_O	S_{FS}	U_{WR}	U_B	U_O	S_{FS}	U_{WR}	U_B	U_O
N=600																
None	4.5	4.5	4.5	4.1	99.9	99.9	99.9	100	100	100	100	100	98.6	98.6	98.6	99.8
Stroke	4.9	4.9	4.9	4.4	100	100	100	100	100	100	100	100	100	100	100	100
Hospitalization	4.9	4.9	4.7	4.8	99.9	99.9	99.9	100	100	100	100	100	99.9	99.9	99.9	100
KCCQ	5.5	5.6	5.5	5.4	68.9	68.9	68.7	74.1	50.3	50.5	49.7	54.5	52.8	52.8	52.5	55.1
Stroke/Hospital	5.3	5.1	5.0	5.0	99.9	99.9	99.9	99.9	100	100	100	100	100	100	100	100
N=400																
None	6.0	6.0	5.9	5.7	99.0	99.0	99.0	99.9	98.7	98.6	98.6	100	98.4	98.4	98.4	99.8
Death	5.1	5.2	5.0	5.7	99.0	98.8	98.9	100	99.5	99.4	99.4	99.9	99.4	99.4	99.4	100
Stroke	5.8	5.8	5.8	5.3	99.0	99.0	99.0	100	99.5	99.5	99.5	100	99.4	99.4	99.4	100
Hospitalization	5.7	5.7	5.7	5.4	99.8	99.8	99.8	99.9	99.8	99.7	99.7	99.9	99.7	99.7	99.7	99.9
KCCQ	5.4	5.4	5.4	5.1	53.1	53.1	52.4	57.7	36.5	36.6	36.1	40.5	36.5	36.8	35.9	39.6
Stroke/Hospital	5.2	5.2	5.1	5.1	99.8	99.8	99.8	99.8	99.7	99.7	99.7	99.7	99.5	99.5	99.5	99.5
N=300																
None	5.6	5.6	5.6	6.3	94.7	94.3	94.3	99.1	95.7	95.7	95.6	99.1	94.9	94.8	94.8	98.2
Death	5.4	5.4	5.4	5.3	96.0	95.9	95.8	99.5	97.5	97.4	97.4	99.8	97.3	97.2	97.1	99.4
Stroke	6.0	6.0	5.9	6.2	96.7	96.5	96.4	99.4	97.6	97.6	97.6	99.7	97.7	97.7	97.6	99.5
Hospitalization	5.4	5.3	5.2	5.2	98.8	98.8	98.7	99.2	98.8	98.8	98.8	99.4	98.6	98.5	98.3	98.9
Stroke/Hospital	6.4	6.4	6.2	6.2	97.7	97.7	97.6	97.6	98.2	98.2	98.2	98.2	98.0	97.9	97.8	97.8
N=200																
None	3.8	3.8	3.4	3.5	83.1	82.6	82.1	95.7	85.7	85.4	85.0	94.5	85.0	84.8	84.1	93.0
Death	6 .0	5.9	5.7	4.8	84.8	84.2	83.7	97.0	88.4	88.1	87.8	95.7	86.3	85.4	85.1	93.3
Stroke	5.6	5.5	5.3	6.0	86.1	85.9	85.5	96.3	87.2	87.1	86.8	95.1	87.6	87.4	87.4	95.1
Hospitalization	4.8	4.8	4.7	4.4	91.0	90.6	90.5	94.0	92.0	91.5	91.2	94.0	91.1	91.0	90.4	93.6
Stroke/Hospital	4.9	4.9	4.2	4.2	90.5	90.2	89.5	89.5	91.9	91.8	90.9	90.9	91.1	90.8	90.6	90.6
N=100																
None	6.0	5.9	5.3	5.5	54.7	53.2	52.2	69.7	56.0	54.9	52.9	69.0	57.4	56.2	55.1	68.3
Stroke	4.4	4.3	3.8	3.5	55.6	55.4	54.1	72.6	62.0	61.4	60.0	73.9	63.3	62.6	60.9	72.3
Hospitalization	3.7	3.6	3.3	3.0	64.6	64.3	61.9	67.2	67.4	66.8	65.2	69.8	66.2	65.9	64.1	68.8
Stroke/Hospital	4.0	4.3	3.2	3.2	64.0	63.3	61.6	61.6	65.0	64.7	62.2	62.2	61.1	60.5	58.6	58.6

Conclusions

Conclusions

- Non-parametric Generalized Pairwise Comparison tests allow to take account of **multiplicity, importance and severity** of events
- Multiple **type of events** (time, continuous, count,..) can be combined
- **Time to first** or **time to worst** event analysis is **equal**
- Generalized Pairwise Comparison tests are **better powered** compared to the classical **logrank** time to first event analysis if non time to event data is added
- There is **little difference** in terms of power between the **hierarchical tests**
- The non-hierarchical **adapted O'Brien** test is **better powered** than the hierarchical tests in certain cases

Further research

- Different **variance** formula's (U-statistics, permutation distribution, non-parametric bootstrap,…)
- Effect of **correlation** between components of composite endpoint
- Effect of non-proportional hazards, unequal sample size, unequal variance, informative censoring
- Effect of **missingness** (completely, partial)

Further research

- Only one **scoring system** applied, alternatives are:
  - Adaptive scoring or weighting of components
  - Peto-Peto[1], Tarone-Ware[2], Efron[3], Péron[4]

- Compare to **other methods** for composite endpoints:
  - Joint distribution models[5,6] (parametric)
  - Competing risk
  - Negative binomial regression

1. Peto et al. *J Royal Stat Soc* (1972) 135: 185-207
2. Tarone et al. *Biometrika* (1977) 64: 156-160
3. Efron. *Proc 5th Berkeley Symp* (1967) 4: 831-853
4. Péron et al. *Stat Methods in Med Research* doi: 10.1177/0962280216658320
5. Vonesh et al. *Stat in Med* (2006) 25: 143-163
6. Alonso et al. Chapmann & Hall/CRC (2017)

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