Win Ratio: A New Approach to the Analysis of Composite Endpoints in Clinical Trials based on Clinical Priorities

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Topics

- Composite endpoint and its problem
- Our new approach
- Results from three clinical trials
- Questions

Composite endpoint and its problem

- Major RCT's in CV disease use composite endpoints as the primary outcome to assess the treatments efficacy
  - Mixture of two or three types of clinical events (e.g., CV death, non-fatal MI, non-fatal stroke etc)
  - Analysis focuses on time to the first event
    - Usually Cox model, KM plots, log-rank tests used for reporting treatment effects
- Implicitly treat all contributory endpoints as equal
- Typically only takes account of the first occurring endpoint
  - Non fatal events occurring earlier in follow-up tend to get a higher priority than later more serious events and deaths

Our New Approach

- Takes into account clinical priorities
  - CV deaths are considered more important than non-fatal events and get first priority
- Recognises that patients have widely different risk profiles
  - Risk-matched pairs are used in the analysis
- Method is easy to use
- Provides a novel estimate of the treatment difference with CI and P-value

Details of the New Method (1)

- Consider the following RCT
  - Superiority trial
  - Comparing new vs standard treatment
  - Uses a composite primary endpoint consisting of CV death and hospitalisation for chronic heart failure (CHF)
  - 1:1 randomisation
- Recognises the (obvious) fact that CV death is a more important event than CHF hospitalisation
- Recognises that patients have widely different risk profiles

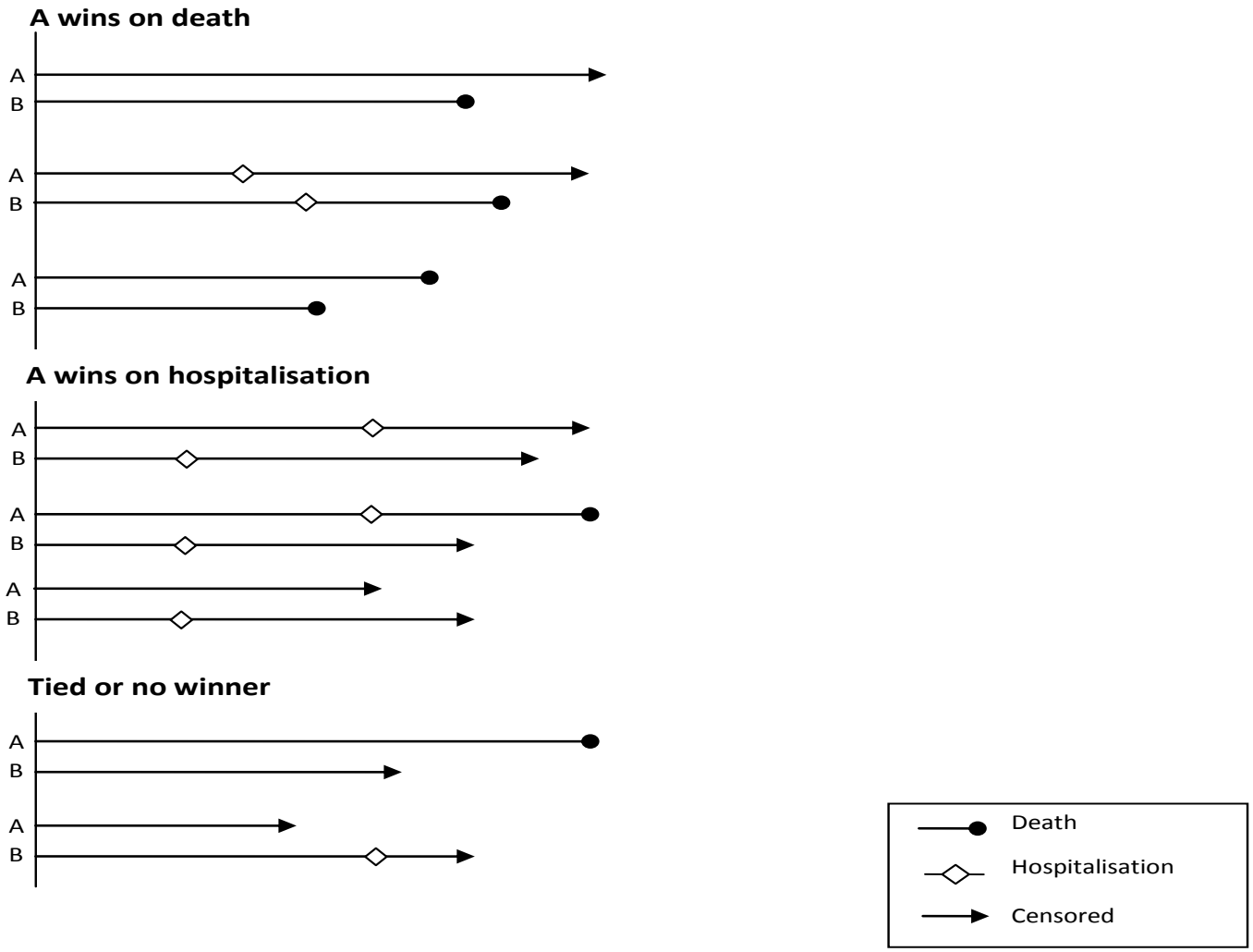
Details of the New Method (2)

- Comparing patients on the new treatment vs patient on standard treatment
  - Did either one have a CV death before the other?
  - If neither had a CV death which patient had a CHF hospitalisation first?
  - Essence of the approach
- Risk stratification is used to account for the underlying risk of the composite endpoint
  - Avoids unfair comparisons
  - Facilitates the creation of matched pairs

Details of the New Method (3)

- Matched Pairs Approach
  1. Matched pairs are formed
     - Matching method will vary – recommend individual patient risk matching
  2. For each pair determine which of the following categories the pair falls into:
     a. New patient had CV death first
     b. New patient has CHF hosp first
     c. Neither of a, b, d or e
     d. Standard patient had CHF hosp first
     e. Standard patient had CHF hosp first
  3. Calculate N_a, N_b, N_c, N_d & N_e the number of matched pairs in each category

How Outcomes Are Determined



Details of the New Method (5)

- Trial findings can be summarised using the five values of N_a, N_b, N_c, N_d & N_e
- The treatment difference can be summarised by the win ratio estimator
- The win ratio for the new treatment is calculated as follows
  - $N_w = N_d + N_e$ are the number of “winners” for the new treatment
  - $N_L = N_a + N_b$ are the number of “losers” for the new treatment
  - The summary estimate is $R_w = N_w / N_L$ is the “win ratio”

Details of the New Method (6)

- The CI and P-value are then calculated as follows
  - A CI for the proportion winning $p_W = N_w / (N_W + N_L)$ is calculated using the regular CI for a binary proportion
    - $p_W \pm 1.96(p_W(1-p_W)/(N_W + N_L))^{½} = (p_L, p_U)$
  - This is then transformed back to a CI for R_w
    - $p_L / (1-p_L)$, $p_U / (1-p_U)$
- A test of the hypothesis of $R_w = 1$ is equivalent to a test of the binomial proportion $p_W = ½$
  - $Z = (p_W - ½) / (p_W(1-p_W)/(N_W + N_L))^{½}$ where Z is a standardised normal deviate under the null hypothesis

Details of the New Method (7)

- Unmatched Approach
  - In some cases matching may not be possible so an unmatched version of the approach is as follows
  - Let N_n and N_s be the number of patients in the new and standard treatment groups respectively
    1. Perform all possible N_n x N_s pair wise comparisons
    2. As for the matched analysis each pair is placed into one of categories a, b, c, d, or e
    3. Calculate N_a, N_b, N_c, N_d & N_e the number of all pairs in each category except here
       - $N_a + N_b + N_c + N_d + N_e = N_n \times N_s$
  - As before the summary estimate R_W is computed

Details of the New Method (8)

- Unmatched Approach
  - No simple method exists to find the CI for R_W
    - We computed a CI using the Boostrap
  - Finklestein and Schoenfeld (Stats in Medicine, 1999) developed a non-parametric significance test for the unmatched case

Example: EMPHASIS HF

- Compared eplerenone v placebo in 2737 patients with NYHA class II HF and ejection fraction ≤ 35%
- Primary outcome was a composite of CV heath or HF hosp
- Reported results:
  - 21 months median follow up
  - 18.3% v 25.9% primary outcome in the eplerenone and placebo groups respectively
  - Hazard ratio 0.63 (95% CI 0.54 – 0.74), P = 0.002
- Issue with conventional analysis is the HF hosp tend to occur first and so the impact of eplerenone on CV death is lost in the composite

Example: EMPHASIS HF

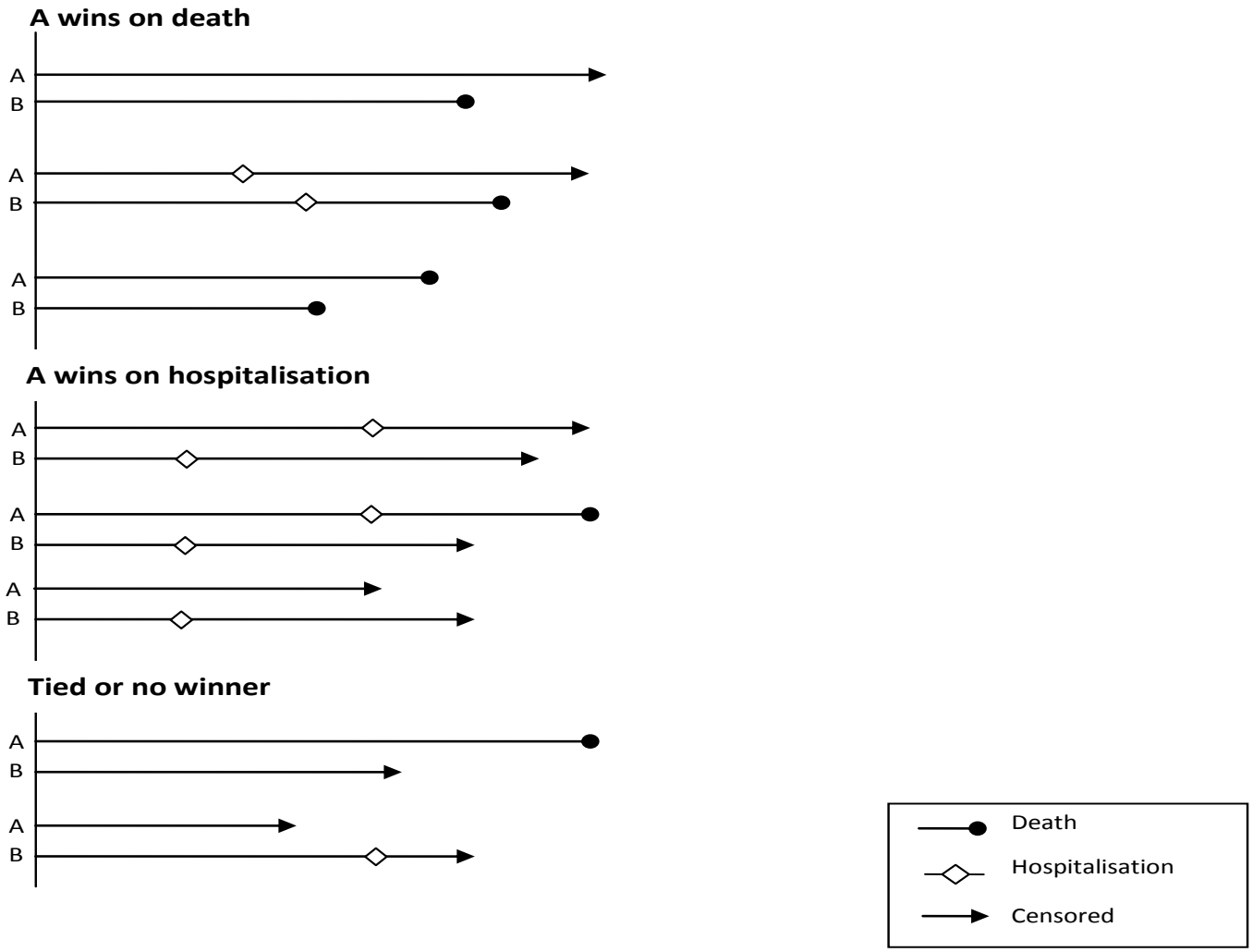
- The new approach was applied in three ways

1. Matched Pairs
   - A risk score was built based on the 9 baseline variables in the original Cox model (excluding treatment)
   - Due to unequal sample size in the eplerenone and placebo groups 9 patients were dropped from the placebo group
   - Patients were then ranked from highest risk to lowest risk in each group based on the risk score
   - Each patient in the eplerenone group was then paired off against the same ranked patient in the placebo group

Results: EMPHASIS HF

	Matched Pairs	Matched Pairs Time Stratified	All Unmatched Pairs
a) CV death on eplerenone first	90	105	124825
b) HF hosp on eplerenone first	61	60	86127
c) none of the other 4 categories	964	914	1323085
d) HF hosp on placebo first	131	137	175606
e) CV death on placebo first	118	148	163129
Total No. of Pairs	1364	1364	1872772
Win ratio for composite	1.65	1.73	1.61
(95% CI)	(1.35, 2.03)	(1.43, 2.10)	(1.37, 1.89)
z-score	5.05	5.87	5.45
Win ratio for CV death only	1.31	1.41	1.31
95% CI	(1.00, 1.74)	(1.10, 1.82)	(1.04, 1.66)
z-score	1.96	2.74	2.25

How Outcomes Are Determined



Example: EMPHASIS HF

2. Matched Pairs, Time Stratified
   - Patients were grouped into five equal strata based on their randomisation date
   - Patients were then risk matched within each time strata
   - This was an attempt to avoid “wasting” events where patients with very different follow up times were paired
   - Using time stratification reduced the number of “wasted” CV deaths from 68 to 30, and “wasted” CHF hospitalisations from 82 to 38 compared to the matched pair analysis

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Example: EMPHASIS HF

3. Unmatched Pairs
   - Each patient in the eplerenone group was compared with every patient in the placebo group
   - This leads to 1364 x 1373 = 1872772 unmatched pairs

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Summary

- There is a need to re-think the way composite endpoints are utilised in major trials
- The win ratio provides an enterprising and clinically relevant of giving priority to the more major components of any composite, e.g., mortality
- The win ratio is conceptually simple and straightforward to apply

Reference

Pocock SJ, Ariti CA, Collier TJ, Wang D.
The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2011 Sep 6 [Epub ahead of print].

Questions?