Application of Win Ratio in Clinical Trials

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Outline

- Background
- Win Ratio
- Examples of WR in Clinical Trials
- Considerations in Clinical Trial Design
- Discussion

Background

- Efficacy in clinical trials in therapeutical areas such as cardiovascular disease is often evaluated through a primary composite endpoint of multiple components
  - Lower event rate in a single endpoint may result in large and often impractical sample sizes
- Conventional statistical methods
  - focus on time-to-event of the first occurrence
  - Difference in clinical severity ignored

Win Ratio

- The win ratio was introduced by Pocock et al. in 2012
  - Taking into consideration of hierarchical nature of the components
    - Subsequent component is compared within any pair of individuals only if there is a tie after comparing the previous component
  - Accommodating different types of components in one composite endpoint
    - Time to Event or recurrent event
    - Counts
    - Continuous or categorical, etc.
  - No distribution assumption needed

Win Ratio

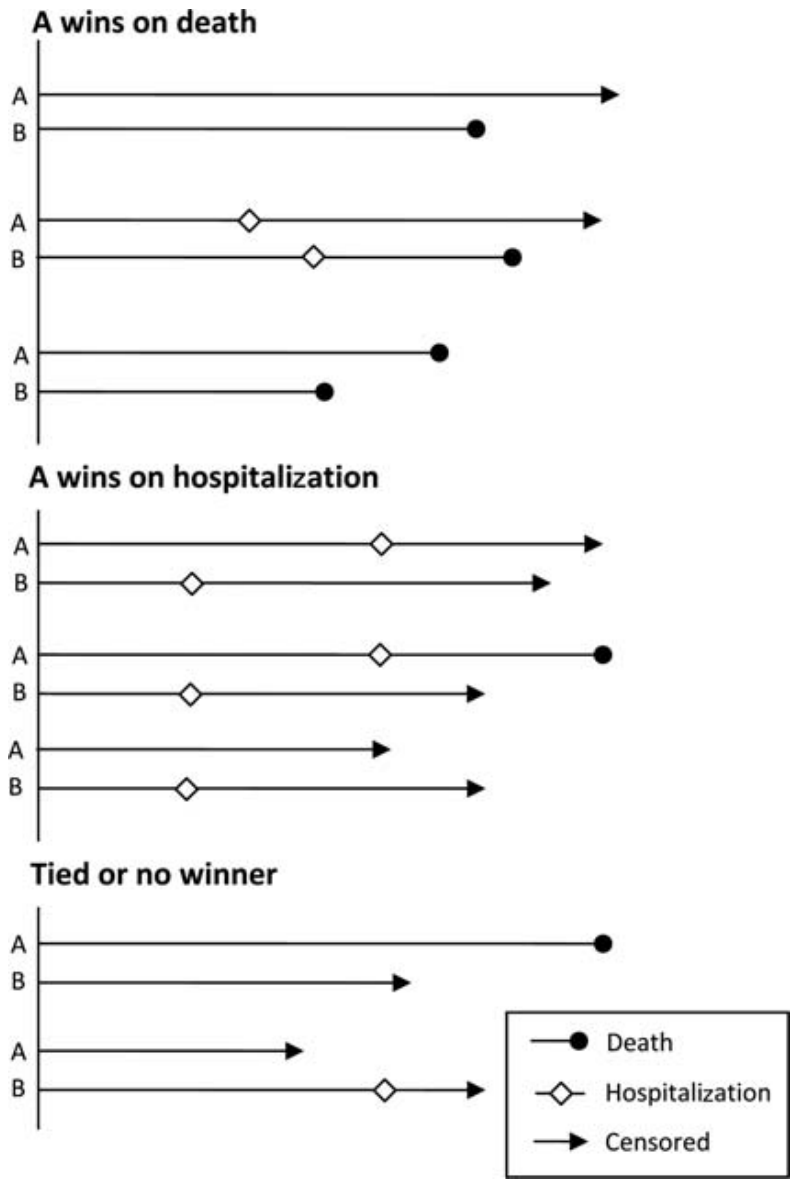
Pairwise comparison between individuals in the treatment and control groups

$$\text{WR} = \frac{N_w}{N_L}$$

where N_w and N_L denote the number of "winners" and "losers", respectively, in the treatment group

- Matched Pair approach
- Unmatched Approach

Pocock et al 2012



Win Ratio

Stratified Win Ratio

$$\text{WR}=\frac{\sum_{m=1}^{M} w^{(m)} n_t^{(m)}}{\sum_{m=1}^{M} w^{(m)} n_c^{(m)}}$$

Where

- $n_t^{(m)}$ and $n_c^{(m)}$ denotes the number wins within the m^{th} stratum for the treatment and control groups, respectively
- $w^{(m)}$ is the weight for the m^{th} stratum
  - Given Mantel-Haenszel weight:

$$\text{WR}=\frac{\sum_{m=1}^{M} n_t^{(m)}/N^{(m)}}{\sum_{m=1}^{M} n_c^{(m)}/N^{(m)}}$$

where $N^{(m)}$ denotes the total sample size in the m^{th} stratum.

Dong et al., 2018

Win Ratio

- Confidence Interval can be rendered in number of ways including
  - Bootstrap approach (Wang and Pocock)
  - analytical approach (Dong et al.)
- Understanding of the WR:
  - pr(treatment better than control)/pr(control better than treatment)
  - How likely are patients in treatment to have a favorable outcome than those in control

Examples of WR in Clinal Trials

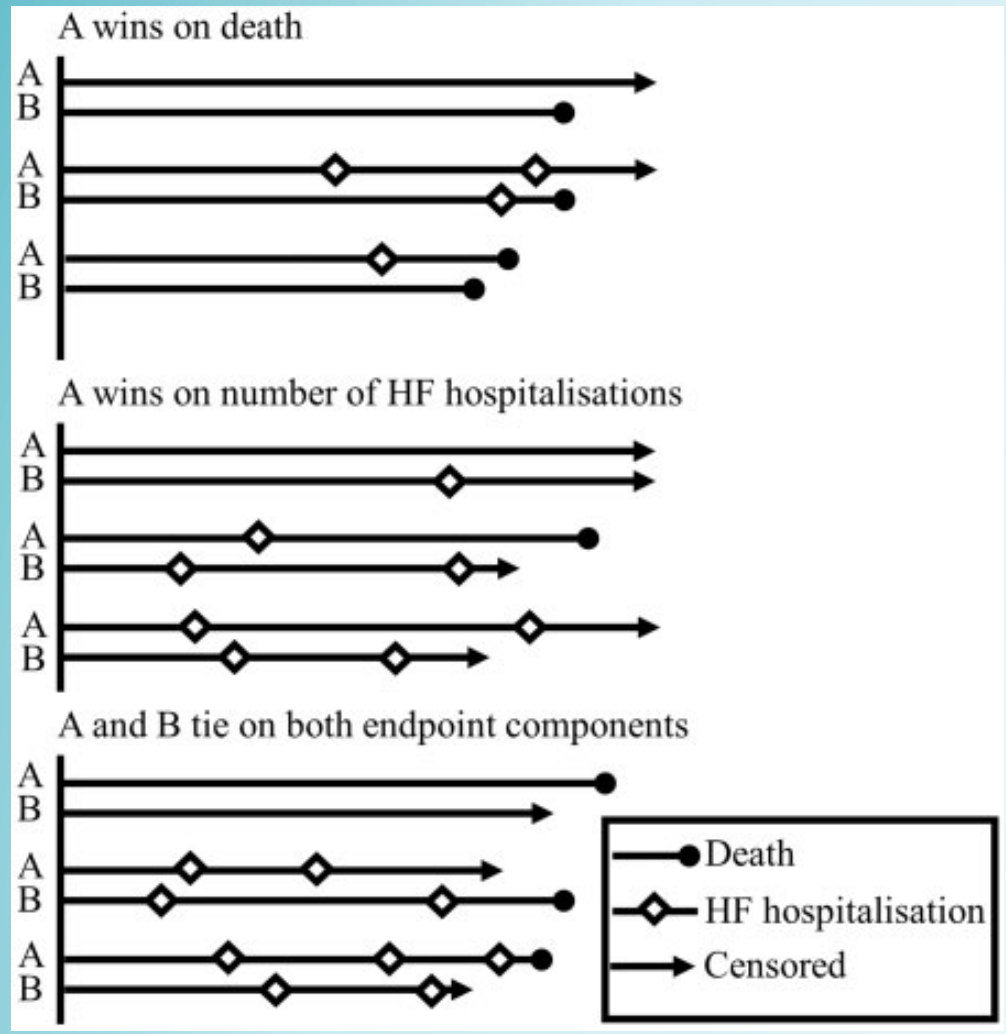
- Win Ratio has grained traction in clinical trials
- ATTR-ACT (tafamidis trial)
  - Primary composite endpoint was proposed to be analyzed by F-S method with WR
  - Trial started in 2013 and completed in 2018
  - NDA approval in 2019

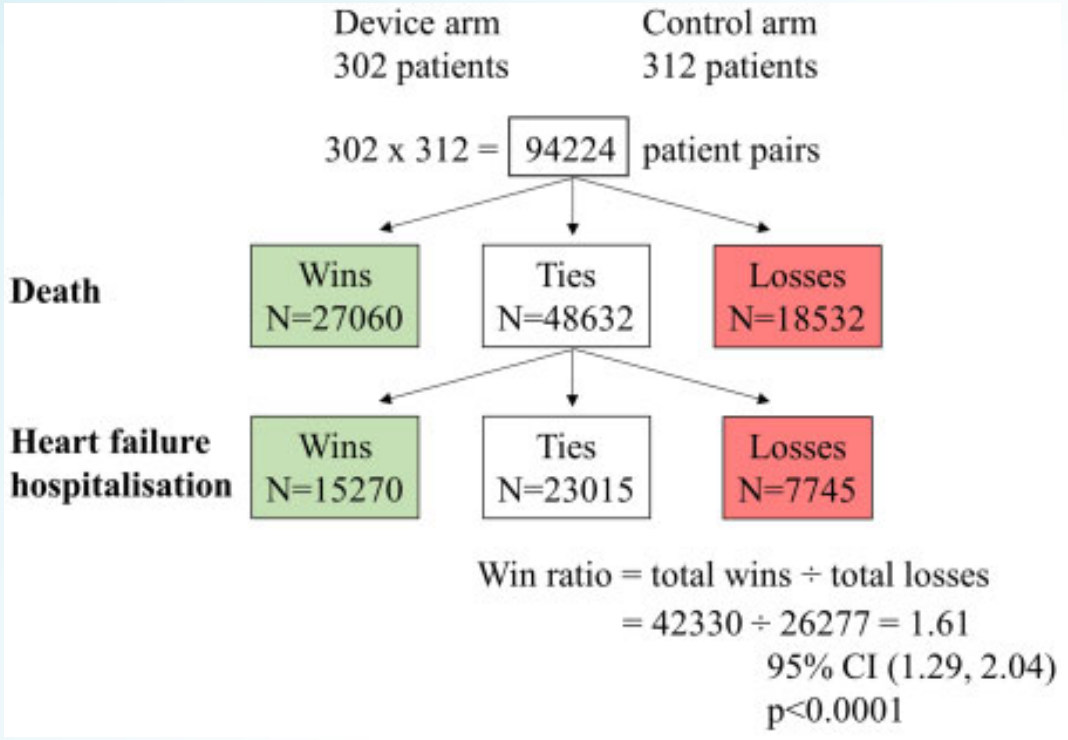
Recent Trials that Have Applided the Win Ratio Approach as the Pre-defined Method

Trial	Population	Randomized treatment	Primary composite endpoint	Win ratio (95% CI)
ATTR-ACT[14]	Transthyretin amyloid cardiomyopathy	Tafamidis vs. placebo	All-cause mortality > number of heart failure hospitalizations	1.70 (1.26–2.29)
CHART-1[16]	LVEF ≤35%	Cardiopoietic stem cells vs. placebo	Time to death > N of HF events > MLHFQ score ≥10-point improvement > 6MWT improvement ≥40 m > LVESV change ≥15 mL > LVEF change ≥4%.	1.17 (0.89–1.55)
TAVR-UNLOAD[18]	Moderate AS and reduced LVEF	TAVR vs. medical therapy	Time to death > disabling stroke > hospitalizations due to HF, aortic valve disease, or non-disabling stroke > change in KCCQ relative to baseline	Ongoing
RELIEVE-HF (NCT03499236)	NYHA class III and IV heart failure	Inter-atrial shunt vs. medical therapy	Time to death > time to heart transplant or LVAD > number and time of hospitalizations due to HF > improvement in 6MWT	Ongoing
CARILLION (NCT03142152)	Functional MR associated with HF	Carillion implant vs. medical therapy	Death > cardiac transplantation or LVAD > percutaneous or surgical mitral valve intervention > time to first HF hospitalization > improvement in 6MWT	Ongoing
ACTIVE (NCT03016975)	Functional MR associated with HF	Cardioband implant vs. medical therapy	Death > number of HF hospitalizations > improvement in 6MWT > improvement in KCCQ	Ongoing
PARACHUTE-HF (NCT04023227)	HF with reduced LVEF caused by chronic Chagas disease	Sacubitril/valsartan vs. enalapril	CV death > HF hospitalization > relative change in NT-proBNP from baseline to week 12	Ongoing

Redfors et al., 2020

An Illustration example





- (Redfors et al., 2020)

Consideration in Clinical Trial Design

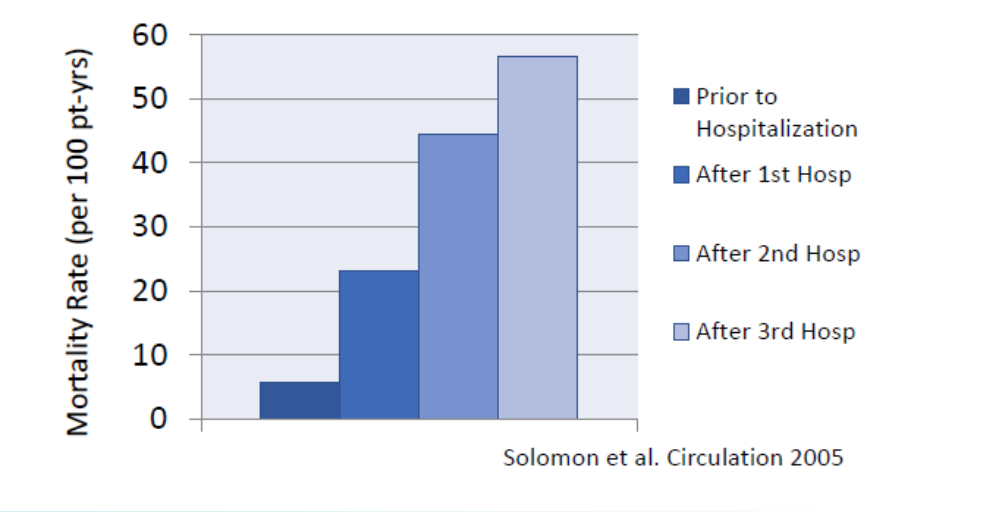
- Choice of Components
  - Clinical relevance
  - Type of components
  - Number of components
- Study follow-up time
- Estimand framework
  - Treatment policy plausible?
- Power considerations

Consideration in Clinical Trial Design – A Case Study

- Primary composite endpoint:
  - 1st component: All-Cause Mortality (ACM)
    - Including CMAD and Heart Failure
    - Time to event: an individual A is a winner compared to B if
      - B has an event before A is censored
      - A has a later event time than B
    - All individuals will be followed up for survival status by end of the trial

Consideration in Clinical Trial Design – A Case Study

- Primary composite endpoint:
  - 2nd component: Cardiovascular-related Hospitalization (CVH)
    - Time to first CVH or cumulative frequency of CVH
      - Clinically meaningful
      - What happens after the first event also matters



Consideration in Clinical Trial Design – A Case Study

- Primary composite endpoint:
  - 3rd component: Functional endpoint such as 6MWT
    - Continuous variable
    - Change from baseline at the last timepoint both have assessments
    - Does the extend of difference matter?
      - Is 0.1 meter difference in change of baseline meaningful?

Consideration in Clinical Trial Design – A Case Study

- Power simulation
  - Knowledge of treatment effect in each component
  - Assumption of distributions
- Understanding contribution of each component
  - Breakdown of ties after each component
  - Calculating WR for the first two components
  - Analysis of each individual component

Discussion in Clinical Trial Design

- Power considerations
  - Ideally, components at higher hierarchy level are expected to have large treatment effect
    - Important components “dominate” the WR
  - In practice, components of lower clinical importance are added with the hope to increase power
    - “Tie breaker”
- Censoring
  - Information is censored by the shorter of the follow-up time in any pair of individuals
  - Every effort should be made to obtain information during the designed follow-up time
  - Taking censoring into consideration of the winning algorithm

Reference

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