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Marlo Thomas GEC Board Room

The Win Ratio and Beyond

Evolution, Applications, and Open Questions in Composite Endpoint Analysis

Lu Mao

lmao@biostat.wisc.edu

Department of Biostatistics & Medical Informatics

University of Wisconsin-Madison

Outline

- Introduction
- Properties and Use Cases
- Extensions and Variations
- Challenges and Open Questions
- Conclusion

Introduction

Composite Endpoint

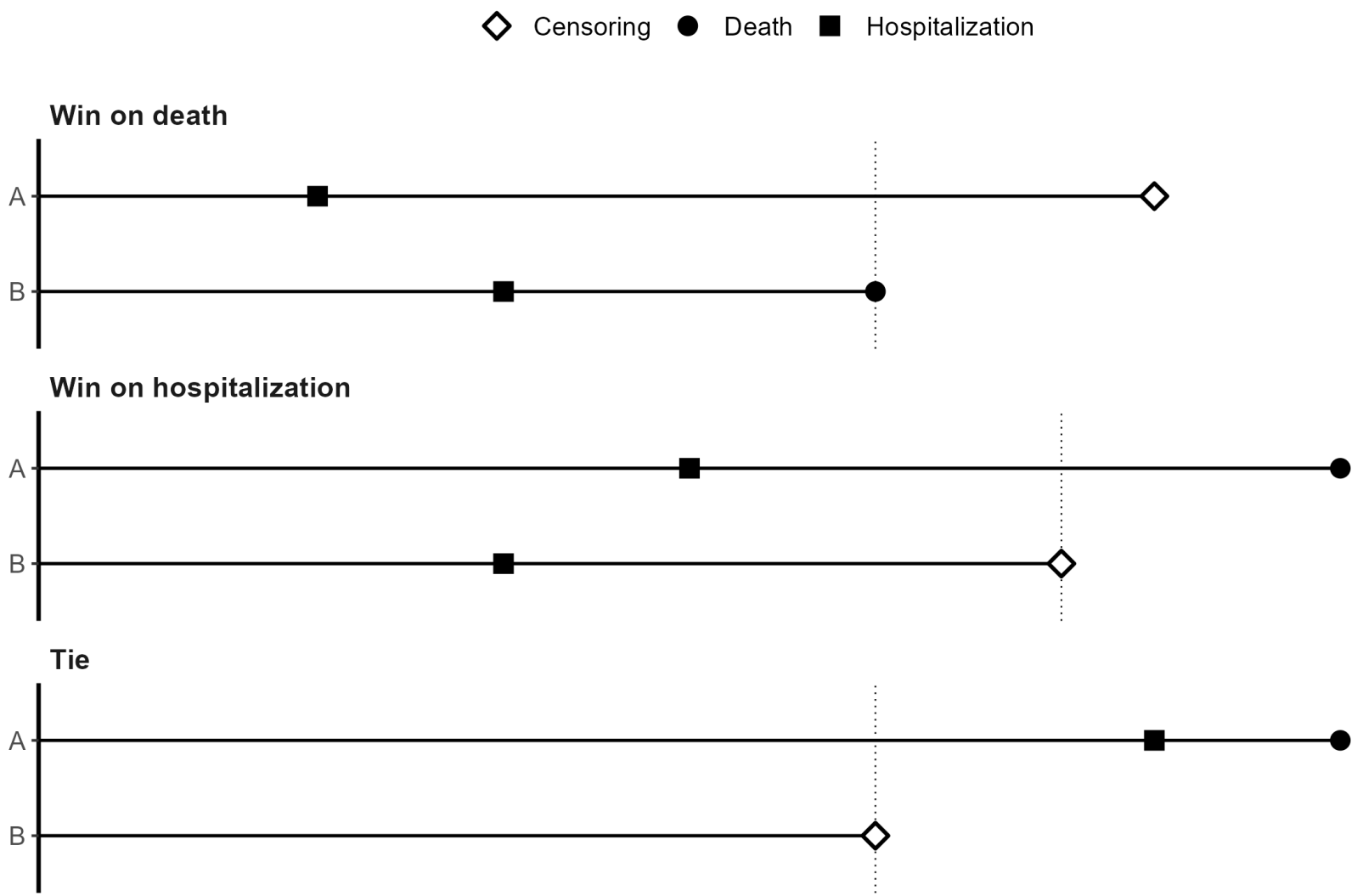
- **Traditional composite endpoint**
  - **Time to first event**
    - Major adverse cardiac event (MACE): death, heart failure, myocardio-infarction, stroke, etc.
  - **Limitations**:
    - Lack of clinical priority
    - Statistical inefficiency (waste of data)
- **Hierarchical composite endpoint (HCE)**
  - **Example**: Death > nonfatal MACE > six-minute walk test (6MWT)/ NYHA class

Win Ratio: Basics

- **A common HCE**
  - **Proposed and popularized** by Pocock et al. (2012)
  - **Treatment vs control**: generalized pairwise comparisons (GPC) (Buyse et al., 2025)
    - **Win-loss**: Longer survival $\rightarrow$ fewer/later nonfatal MACE $\rightarrow$ better 6MWT/NYHA
  - **Effect size**: WR $=$ wins / losses
    - Fold increase in probability of winning over lossing
- **Alternative metrics**
  - **Net benefit** (Proportion in favor): NB $=$ wins $-$ losses (Buyse, 2010)
  - **Win odds**: WO $=$ (wins $+ 2^{-1}$ties) / (losses $+ 2^{-1}$ties) (Brunner et al., 2021)

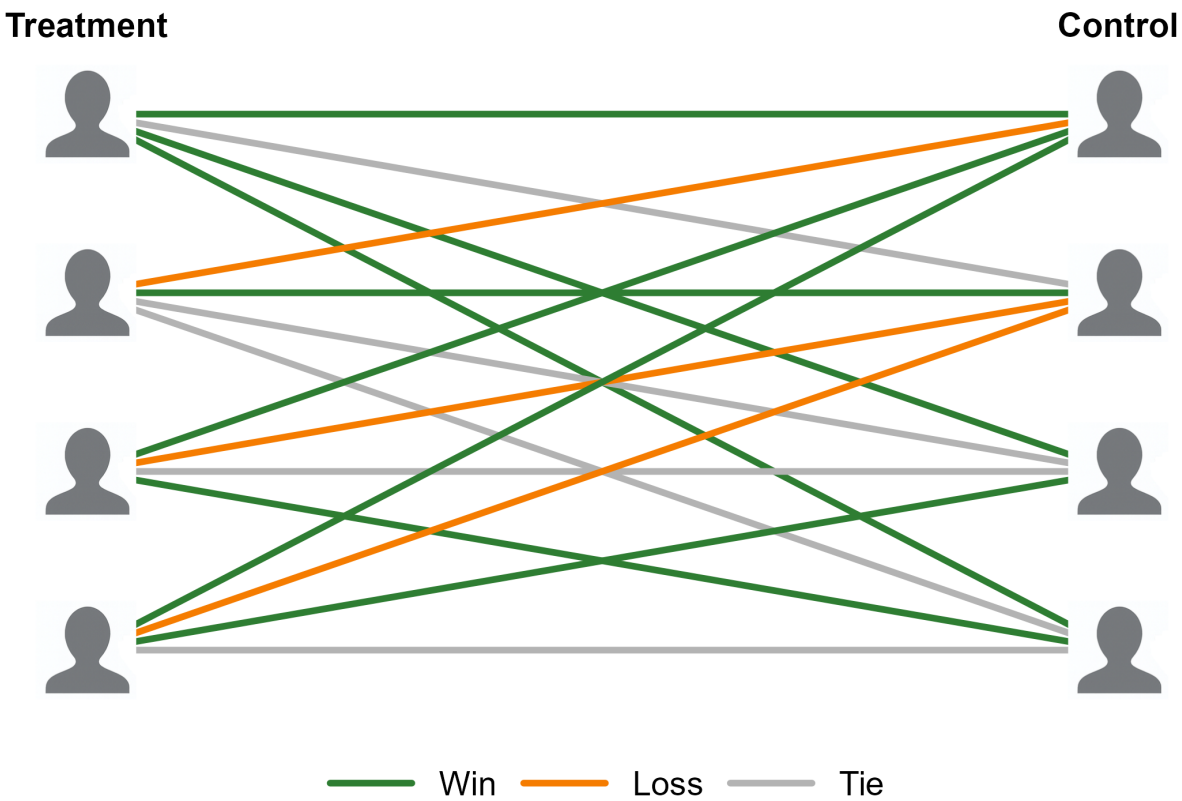
Prioritized Comparison

Cut off at earlier end of follow-up



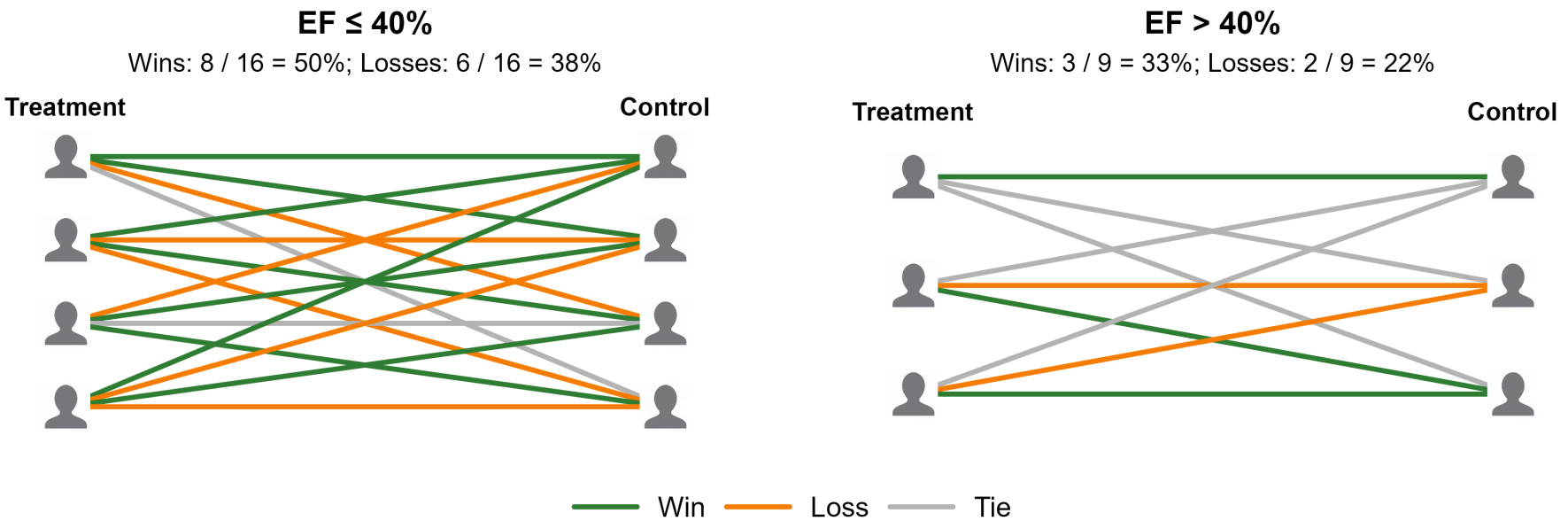
Pairwise Comparison

- **GPC Results**
  - Wins: 8 / 16 = 50%
  - Losses: 3 / 16 = 18.8%
  - Ties: 5 / 16 = 31.2%
- **Effect Sizes**
  - WR = 50% / 18.8% = 2.67
  - NB = 50% - 18.8% = 31.2%
  - WO = (50% + 15.6%) / (18.8% + 15.6%) = 1.72



Stratification

- **GPC within stratum and aggregate** (Dong et al., 2018, 2023)



$$\text{Wins: } 50\% \times 8/(8+6) + 33\% \times 6/(8+6) = 42.7\%$$
$$\text{Losses: } 38\% \times 8/(8+6) + 22\% \times 6/(8+6) = 31.1\%$$

- **Overall WR:** 42.7% / 31.1% = 1.37

Properties and Use Cases

General Setting

- **Notation**
  - n_1, n_0: sample sizes in treatment and control
  - W_{ij}: win-loss indicator of subject i in treatment vs j in control

$$W_{ij} = \begin{cases} 1, & \text{if subject } i \text{ in treatment wins} \\ -1, & \text{if subject } j \text{ in control wins} \\ 0, & \text{if tie} \end{cases}$$

    - Wins : $\hat{w}_{1,0} = (n_1 n_0)^{-1} \sum_{i=1}^{n_1} \sum_{j=1}^{n_0} I(W_{ij} = 1)$
    - Losses : $\hat{w}_{0,1} = (n_1 n_0)^{-1} \sum_{i=1}^{n_1} \sum_{j=1}^{n_0} I(W_{ij} = -1)$
  - $\mathrm{WR} = \hat{w}_{1,0} / \hat{w}_{0,1}$; $\mathrm{NB} = \hat{w}_{1,0} - \hat{w}_{0,1}$; $\mathrm{WO} = (1 + \mathrm{NB})/(1 - \mathrm{NB})$

Binary Case Equivalencies

- **Binary outcome, no censoring**
  - $Y_i^{(a)} = 1$ (response) vs 0 (no-response) for subject i in group a ($a = 0, 1$)
  - Win-loss (1-0) fractions

$$\hat{w}^{(a,1-a)} = (n_a n_{1-a})^{-1} \sum_{i=1}^{n_a} \sum_{j=1}^{n_{1-a}} Y_i^{(a)} (1 - Y_j^{(1-a)}) = \hat{p}_a (1 - \hat{p}_{1-a})$$

    - $\hat{p}_a = n_a^{-1} \sum_{i=1}^{n_a} Y_i^{(a)}$ = response rate in group a

- **GPC stats**
  - WR $= [\hat{p}_1(1 - \hat{p}_0)]/[\hat{p}_0(1 - \hat{p}_1)] =$ response odds ratio
  - NB $= \hat{p}_1 - \hat{p}_0 =$ response rate difference

Variance Estimation

- **Bootstrap**
  - Inital proposal (Pocock et al., 2012)
- **Analytic asymptotic variance**
  - Asymptotic decompostion of U-statistics (Bebu & Lachin, 2016; Dong et al., 2016; Luo et al., 2015)
  - Influence function-based
  - **R packages**: `WR`, `WINS`, `BuyseTest`, `WinRatio`, etc.

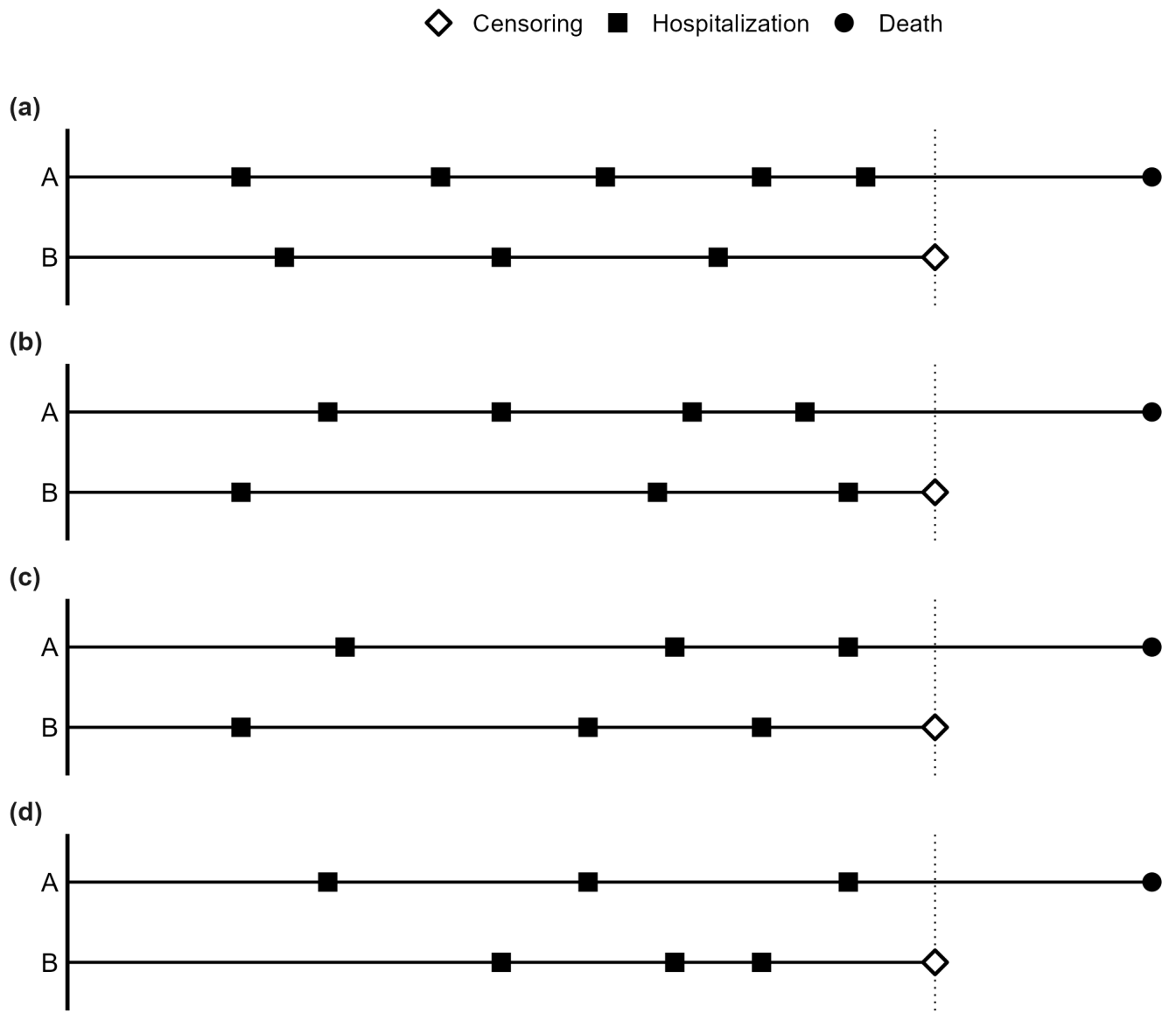
Null vs Alternative Hypotheses

- **Null hypothesis**: No treatment effect on any event
  - WR $= 1$, NB $= 0$, WO $= 1$ regardless of follow-up time
- **Alternative hypothesis**
  - Death and hospitalization times: *stochastically larger* in treatment than in control (Luo et al., 2015; Mao, 2019)
    - Stratified test: Stochastical order in each stratum
  - So WR > 1, NB > 0, WO > 1 regardless of follow-up time
  - Power $\to 1$ as $n = n_1 + n_0 \to \infty$

Recurrent Events (I)

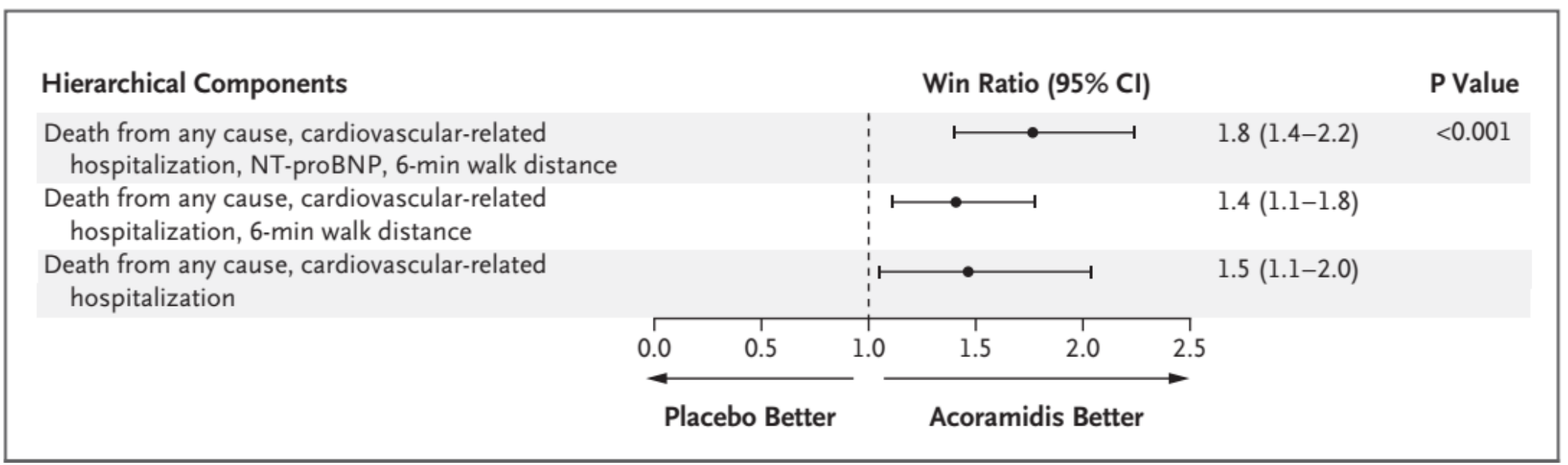
- **GPC to accommodate recurrent events**
  - E.g., hospitalizations, exacerbations, infections, etc.
- **Comparison rules**
  - Death $\rightarrow$ Number of events $\rightarrow$ Time to first/last event (Mao, Kim, & Li, 2022) $\rightarrow$ … (Biomarker/QoL changes)
  - H_A: Treatment stochastically delays all events

Recurrent Events (II)



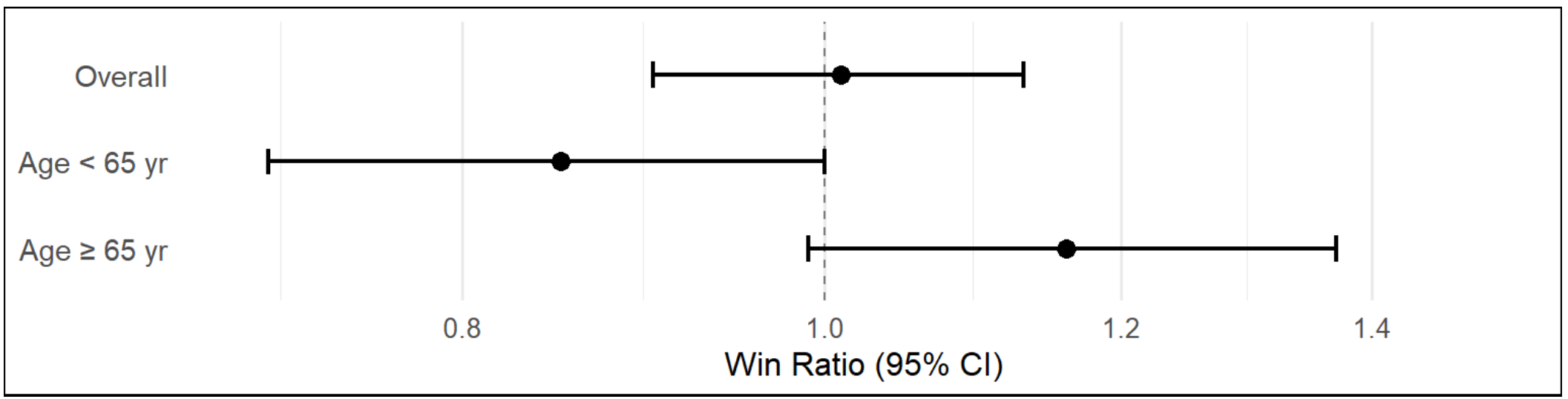
ATTRibute-CM (NEJM 2024)

- **Trial data** (Gillmore et al., 2024)
  - **Design:** Phase 3, double-blind RCT (n = 632; 2:1 randomization)
  - **Population:** Transthyretin amyloid cardiomyopathy (90 % wild-type, mean age 77 yr)
  - **Intervention:** Acoramidis 800 mg BID vs placebo for 30 months
  - **Primary HCE:** Death → CV hospitalization → NT-proBNP → 6-min walk distance
    - Stratified by TTR genotype, NT-proBNP level, eGFR, etc.



DEFENDER (JAMA 2024)

- **Trial data** (Tavares et al., 2024)
  - **Design:** Multicenter, open-label RCT (n = 507; 22 ICUs in Brazil)
  - **Population:** Critically ill adults with an organ dysfunction (respiratory/ cardiovascular/ renal)
  - **Intervention:** Dapagliflozin 10 mg daily vs standard care alone (up to 14 days)
  - **Primary HCE:** Hospital mortality → initiation of KRT → ICU length of stay (28 days)



WR as Primary Endpoint (I)

Gregson et al. (2025) summarizes recent/ongoing RCTs:

Trial	Condition	Interventions	HCE
ATTRibute-CM (2024)	Transthyretin amyloid cardiomyopathy	Acoramidis vs placebo	Death → CV hosp → NT-proBNP/6MWT
COVID-PACT (2022)	Critically ill COVID-19	Full-dose AC vs standard-dose AC	Venous/arterial death → PE → DVT → …
DAPA-MI (2024)	Clinically stable acute MI	Dapagliflozin vs placebo	CV death → non-CV death → HF hosp → …
DEFENDER (2024)	Critical illness with organ failure	Dapagliflozin + SOC vs SOC	In-hospital death → KRT initiation → ICU LOS
EMPULSE (2022)	Acute HF (hospitalized)	Empagliflozin vs placebo	All-cause death → HF events (number/time) → KCCQ change
HEART-FID (2023)	HFrEF with iron deficiency	Ferric carboxymaltose vs placebo	All-cause death → HF hosp → 6MWT change

WR as Primary Endpoint (II)

Trial	Condition	Interventions	HCE
PARTNER 3 (2023)	Low-risk symptomatic AS	TAVR vs SAVR	Death → stroke → rehospitalization days
REDUCE LAP-HF II (2022)	HFpEF/HFmrEF	Atrial shunt device vs sham	CV death/stroke → HF hosp → KCCQ change
TRILUMINATE (2023)	Symptomatic tricuspid regurgitation	TEER vs OMT	Death/surgery → HF hosp → KCCQ change
VIP-ACS (2022)	Acute coronary syndrome	High-dose influenza vaccine vs standard	Death → MI → stroke → …

…

Extensions and Variations

Sample Size Calculation

- **Rank-based approximation** (Yu & Ganju, 2022)

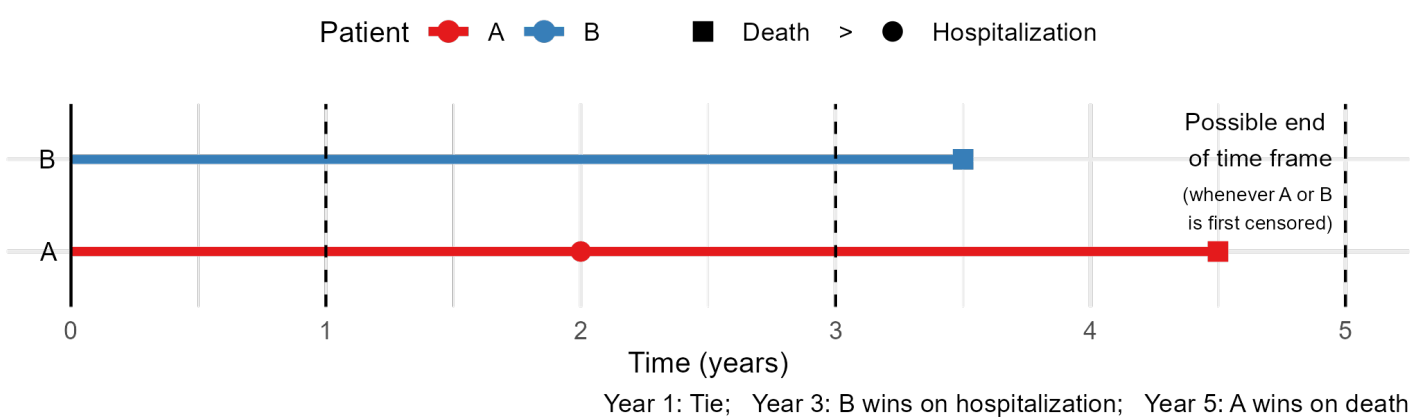
$$n \approx \frac{4(1+p_{\text{tie}})(z_{1-\alpha/2}+z_{1-\beta})^2}{3q(1-q)(1-p_{\text{tie}})\log^2(\text{WR})}$$

  - $\alpha = 0.05$: type I error; $1-\beta = 80\%, 90\%$: desired power
  - $q = n_1/n$; p_{tie}: proportion of ties
  - Elicit effect size $\log(\text{WR})$ and p_{tie} from component-wise win-loss measures (Barnhart et al., 2025a, 2025b)

- **Parametric approach** (Mao, Kim, & Miao, 2022)
  - Gumbel–Hougaard copula + Numerical integration (R package `WR`)

Estimand Issue

- **Without censoring**
  - WR, NB, WO = functions of joint distribution of events
  - Change with follow-up time (Mao, 2024; Oakes, 2016)



- **With censoring**
  - Weighted average of win-loss probabilities over time
  - Trial-dependent estimand (ICH, 2020)

Time Restriction

- **Specify time horizon τ**
  - Imagine all subjects followed up to τ (1 yr, 3 yrs, etc.)
- **GPC under consistent time frame**
  - **Estimand**: WR(τ), NB(τ), WO(τ)
  - **Interpretation**: win ratio/net benefit/win odds up to time τ
- **Estimation with censored data**
  - Inverse probability censoring weighting (Dong et al., 2020b, 2021)
    - **R-package**: `WINS`
  - Multiple imputations (T. Wang et al., 2023, 2024)

Regression Analysis

- **A proportional win-fractions (PW) model**

$$\frac{\mathrm{pr}(W_{ij}(t) = 1 \mid Z_i, Z_j)}{\mathrm{pr}(W_{ij}(t) = -1 \mid Z_i, Z_j)} = \exp\{\beta^{\mathrm{T}}(Z_i - Z_j)\}$$

  - $W_{ij}(t)$: win-loss indicator by time t
  - Z_i, Z_j: covariate vectors for subjects i and j
  - β: log-WRs for one-unit increases in covariates
  - U-statistic estimation; residual analysis to check WR constancy (Mao & Wang, 2021, R package `WR`); stratification (T. Wang & Mao, 2022)
  - Elastic net regularization for high-dimensional Z (Mao, 2025, R tool `WRNet`)

Win-Loss Times

- **Restricted mean time** in favor of treatment

$$\mu(\tau) = w_{1,0}(\tau) - w_{0,1}(\tau)$$

  - $w_{a,1-a}(\tau)$: average *time* subject in group a wins over subject in group $1-a$ up to time τ
  - Interpretation: net favorable time gained/lost by treatment (Mao, 2023, R package `rmt`)

- **Other win time measures**
  - Expected win time ($\tau \to$ maximum length of follow-up), etc. (Troendle et al., 2024)

DOOR

- **Desirability of outcome ranking** (Evans et al., 2015)
  - Pre-defined ordinal categories of clinical outcome $Y^{(a)}$
    1. Dead
    2. Alive with severe AE
    3. Alive with mild AE
    4. Alive without AE
- **Estimand**
  - Tie-adjusted *win probability* from GPC ranked by DOOR

$$\theta_{\text{DOOR}} = \Pr(Y^{(1)} > Y^{(0)}) + \tfrac{1}{2}\Pr(Y^{(1)} = Y^{(0)})$$

  - R package `door`

Challenges and Open Questions

Critiques

- **Some caveats** (Butler et al., 2024)
  - WR ignores ties
    - Win relative to *loss* rather than *"not win"*
    - Some consider this to overstate effect size
  - Inclusion of low-priority biomarker
    - Surrogate measures drives treatment effect
  - Subjectivity in defining HCE
    - Clinical input needed
    - Post hoc construction inflates type I error

Covariate Adjustment

- **Different from regression**
  - **Marginal estimands** between groups, not conditioning on Z
  - **Gain efficiency** when outcome-covariate model is true, otherwise still valid (robustness)
  - **Standard endpoints**
    - Continuous, binary, univariate survival, etc. (Tsiatis et al., 2008; B. Wang et al., 2021; Ye et al., 2023)
    - FDA recommendation (FDA, 2023)
- **Challenges with WR**
  - U-statistic structure
  - Lack of likelihood structure

Interim Analysis

- **Purpose**
  - Analyze interim data for evidence of efficacy/futility $\rightarrow$ stop trial early
  - Univariate survival: information accrued $\propto$ number of events
- **Challenges with WR**
  - Information time not event-driven
    - Case study: RMST (Lu & Tian, 2021; Luo et al., 2019)
  - Correlations between component events
    - *Dependent* increments

Meta Analysis

- **Challenges**
  - Primary studies *not* reporting win-loss measures
  - Primary studies over *different* time spans
  - Primary studies with *different* definitions of win/loss
- `WinKM`: A toolkit to start
  - Calculate win-loss statistics based on
    - KM estimates for OS and EFS
    - At-risk table at selected time points
    - Total event counts (reported in the CONSORT diagram or results section)

Conclusion

Key Takeaways (I)

- **Win ratio and its variants**
  - Intuitive, clinically interpretable effect sizes for HCEs
  - Support recurrent events, stratification, etc.
  - Time-resticted estimands, regression analysis, win times, DOOR, etc.
- **Good practice**
  - Pre-specify HCE definition and analysis plan
  - Caution in including surrogate measures
    - Anticipated clinical event rates
    - Set thresholds for meaningful differences
  - Sensitivity analyses

Key Takeaways (II)

- **R packages**
  - `WR`, `WINS`, `BuyseTest`, `WinRatio`, `rmt`, `WRNet`, `door`, `WinKM`, etc.
- **Open questions**
  - Covariate adjustment, interim analysis, meta analysis, etc.

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