The popular **win ratio** prioritizes composite outcomes but lacks flexibility to incorporate additional information. Bayesian cumulative probability regression is a solution.

Can we retain important properties of the non-parametric Win Ratio approach with a more flexible Bayesian semi-parametric regression model?

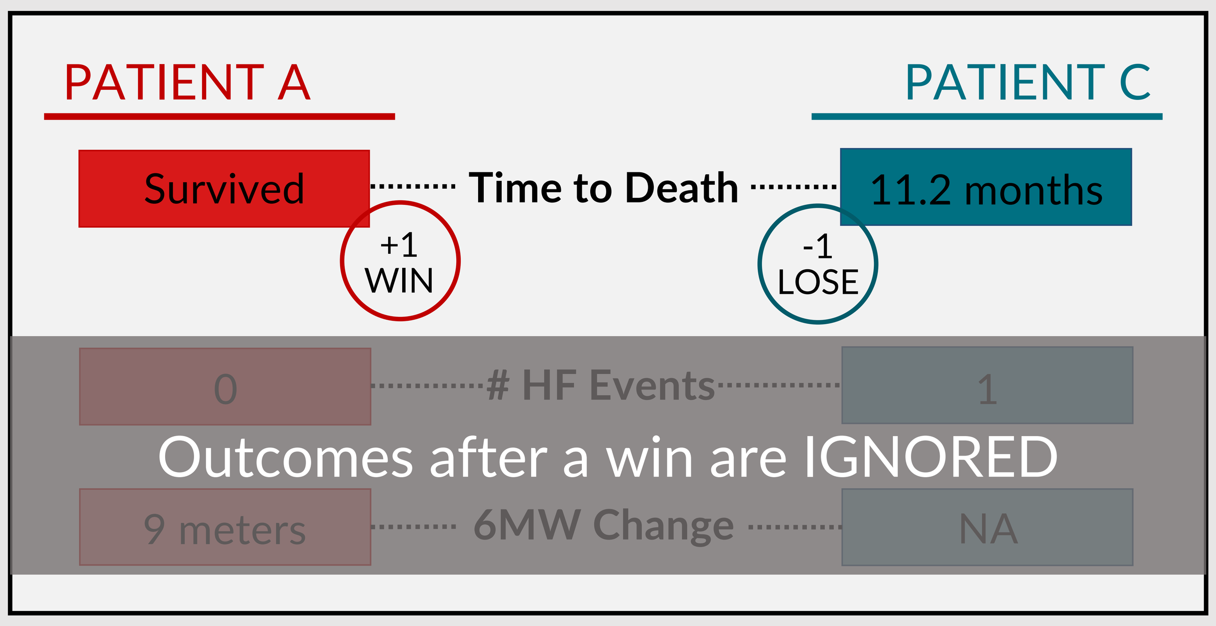
MOTIVATION

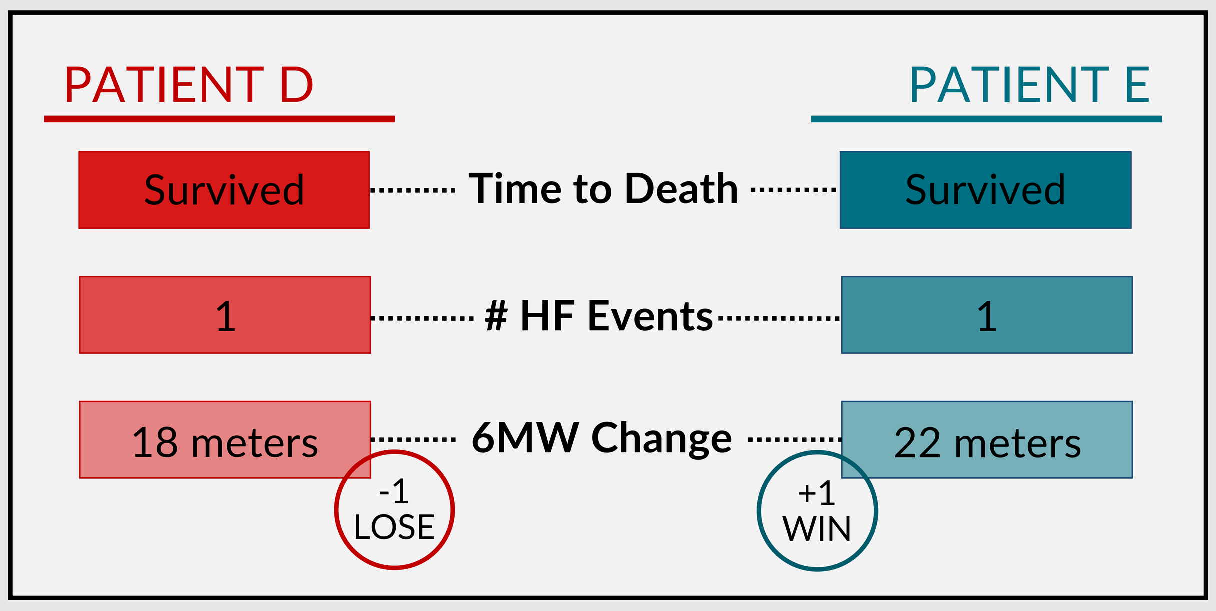
- A **hierarchical composite endpoint** allows major, but infrequent, clinical events to be prioritized over minor, routinely-captured measures (e.g., quality of life).
- With these endpoints, two groups are traditionally compared with a **win-ratio**[1] and a non-parametric **joint rank test** (Finkelstein-Schoenfeld).[2] Both rely on **pairwise comparisons** of patients.
- A **cumulative probability regression model (CPM)** facilitates covariate adjustment and incorporation of external evidence**,** objectives not easily achieved in the joint rank analysis. Can be fit to continuous data.[3, 4]

EXAMPLE: Data

Patient ID	Priority 1: Time to Death (months)	Priority 2: # of HF Events	Priority 3: Six Minute Walk Change (meters)
A	NA	0	9
B	NA	0	30
C	11.2	1	NA
D	NA	1	18
E	NA	1	22

Pairwise comparisons of all patients:





Computing a patient's *balance*

1. Conduct all pairwise comparisons
2. Sum each patient's wins (+1), losses (-1) and ties (0) to get their ***balance***.

BAYESIAN CP MODEL

Take the set of unique patient balances as an **ordinal outcome**. A Bayesian cumulative probability regression model (CPM) is fit to adjust for covariates and incorporate external information.

Justification: The patient balances are clearly dependent (assumption violation). However, if the hierarchical endpoint is transitive, then **there exists an underlying independent variable that is order-generating for the balances.**[5] Bayesian rank analyses often model this variable latently.[6]

- The Bayesian CPM for continuous data evaluates only the order of observations (not values).[7]
- Identical ordering of the independent variable and the dependent balances leads to an identical Bayesian CPM analysis for both.

EXAMPLE: The Bayesian CPM with Historical Borrowing

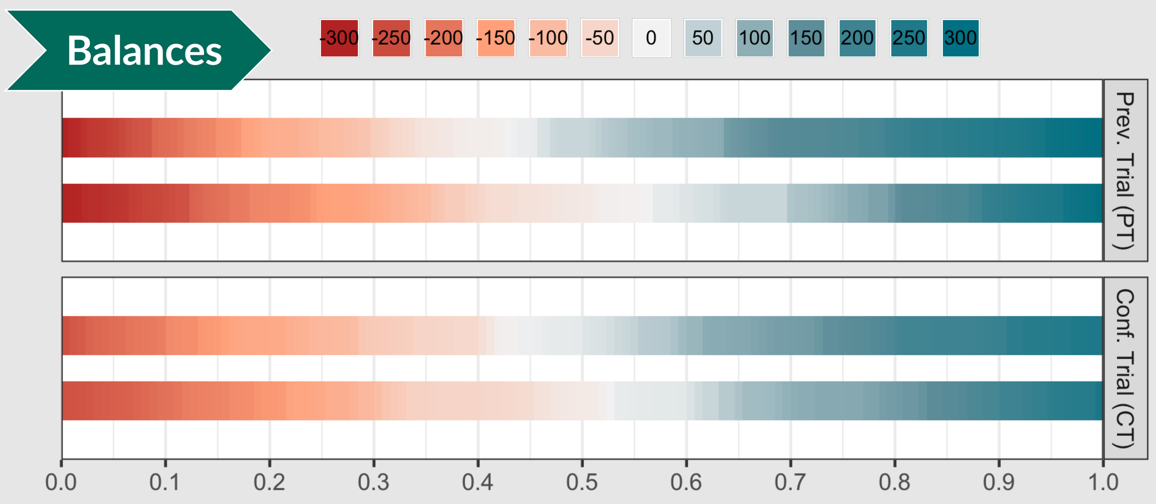
Run a confirmatory trial (CT) with the 3-level hierarchical endpoint and borrow treatment effect information from a previous, positive trial (PT) in the same population.[8]

Do treated patients tend to fare better than control patients?

Data Summaries

	PT (n = 300)		CT (n = 260)	
	Ctrl	Treat	Ctrl	Treat
# of Deaths	1	0	2	0
# of HFE in 12m	33	22	28	18
6MW Change Mean	28m	43m	32m	44m

Balances

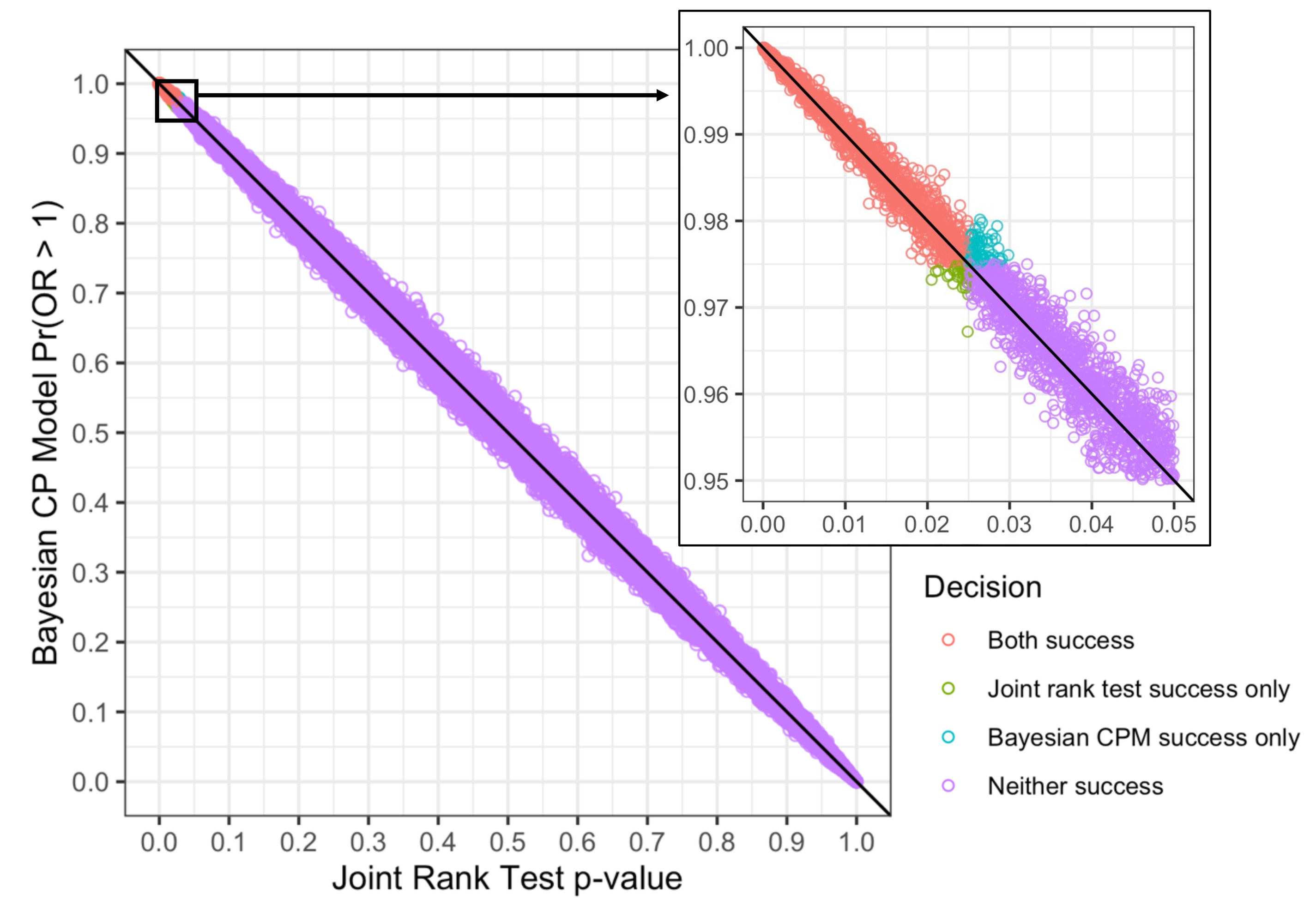


Results

Trial	Bayesian CPM with 30% borrowing OR (95% CI); Pr(OR > 1)	Bayesian CPM Independent analyses OR (95% CI); Pr(OR > 1)	Joint rank test result Independent analyses p-value
PT (n = 300)	1.50 (1.06, 2.14); 0.988	1.68 (1.16, 2.44); 0.9931	0.0064
CT (n = 260)		1.42 (0.92, 2.17); 0.9430	0.0536

COMPARISON: Bayesian CPM vs. Joint Rank Analysis

- Based on 55,000 simulated clinical trials under the null hypothesis with N = 260.
- Correspondence between the Bayesian CPM for balances and the joint rank test.
- A small proportion (0.002) of trial outcomes disagree (green and blue dots). In those trials, the non-significant test is within ± 0.005 of the threshold.



CONCLUSION

The Bayesian CPM can be used for the pairwise comparison patient balances treated as ordinal outcomes, if the hierarchical endpoint is transitive.

The Bayesian CPM provides a valid and flexible semi-parametric alternative to the win-ratio and non-parametric joint rank analysis for prioritized composite endpoints.

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Cora Allen-Savietta* & Amy Crawford*
*These authors contributed equally to this work.

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